e-ISSN: 2822-4469

OFFICIAL JOURNAL OF THE IZMIR CHILDREN'S HEALTH SOCIETY
AND IZMIR DR. BEHCET UZ CHILDREN'S HOSPITAL

JOURNAL OF BEHÇET UZ CHILDREN'S HOSPITAL

galenos yayınevi

behcetuzdergisi.com

Volume: 14
Issue: 3
DECEMBER '24

JOURNAL OF BEHÇET UZ CHILDREN'S HOSPITAL

2024
Volume: 14
Issue: 3

EDITORIAL BOARD

Publisher Contact
Address: Molla Gürani Mah. Kaçamak Sk. No: 21/1
34093 İstanbul, Turkey
Phone: +90 (530) 177 30 97 / +90 (539) 307 32 03
E-mail: info@galenos.com.tr/yayin@galenos.com.tr
Web: www.galenos.com.tr
Publisher Certificate Number: 14521

Online Publishing Date: December 2024
e-ISSN: 2822-4469
International periodical journal published three times in a year.

JOURNAL OF BEHÇET UZ CHILDREN'S HOSPITAL

2024
Volume: 14
Issue: 3

ADVISORY BOARD

JOURNAL OF BEHÇET UZ CHILDREN'S HOSPITAL

2024
Volume: 14
Issue: 3

ADVISORY BOARD

JOURNAL OF BEHÇET UZ CHILDREN'S HOSPITAL

2024
Volume: 14
Issue: 3

ADVISORY BOARD

JOURNAL OF BEHÇET UZ CHILDREN'S HOSPITAL

2024
Volume: 14
Issue: 3

Please refer to the journal's webpage (**https://behcetuzdergisi.com/jvi.asp**) for "Ethical Policy", "Instructions to Authors" and "Instructions to Reviewers".

The Journal of Behcet Uz Children's Hospital and/or its editors are members of ICMJE, COPE, WAME, CSE and EASE, and follow their recommendations. Journal of Behcet Uz Children's Hospital is indexed by the **Web of Science-Emerging Sources Citation Index, EBSCO Academic Search Database, Google Scholar, Microsoft Academic Search, Ulakbim TR Dizin, Türk Medline, the Turkish Citation Index, J-Gate** and **Cabi**.

Journal of Behcet Uz Children's Hospital is published electronically and has been accepting publications in English.

Owner: İzmir Children's Health Society and Dr. Behcet Uz Children's Hospital

Editor in Chief: Prof. MD. Behzat ÖZKAN

JOURNAL OF BEHÇET UZ CHILDREN'S HOSPITAL

2024
Volume: 14
Issue: 3

Contents / İçindekiler

DOI: 10.4274/jbuch.galenos.2024.22230
J Dr Behcet Uz Child Hosp 2024;14(3):127-134

Review

Impact of Orthodontic Treatment on the Oral Health-related Quality of Life in Children

Ortodontik Tedavinin Çocuklarda Ağız Sağlığına Bağlı Yaşam Kalitesi Üzerindeki Etkisi

Genta Agani Sabah[1], Mehmet Gümüş Kanmaz[2]

[1]İzmir Tınaztepe University Faculty of Dentistry, Department of Orthodontics, İzmir, Turkey
[2]İzmir Tınaztepe University Faculty of Dentistry, Department of Periodontology, İzmir, Turkey

ABSTRACT

Oral health-related quality of life has become an essential measure in dental research and clinical practice, capturing the impact of oral health on an individual's overall well-being across psychosocial domains. In children and adolescents, oral health-related quality of life assessments differ significantly when compared to adults, with a focus on factors like self-image, social acceptance, and school environment. The aim of this article is to present a general review of the relationship between malocclusions and oral health-related quality of life, examining how dental problems, especially those impacting aesthetics, can influence a young patient's social and emotional well-being. It also emphasizes the effectiveness of orthodontic treatment in enhancing oral health-related quality of life particularly in terms of socio-emotional aspects, underscoring patient-centered care. This review advocates for the integration of oral health-related quality of life measures into clinical decisions to better address patients' functional and emotional needs, by improving their overall quality of life.

Keywords: Oral health, quality of life, child health

Received: 15.11.2024
Accepted: 17.11.2024

Corresponding Author
Genta Agani Sabah
İzmir Tınaztepe University Faculty of Dentistry, Department of Orthodontics, İzmir, Turkey
genta.agani@gmail.com
ORCID: 0000-0002-7571-6922

ÖZ

Ağız sağlığına bağlı yaşam kalitesi, ağız sağlığının psikososyal boyutlarda kişinin genel sağlığına etkisini ortaya koymasıyla diş hekimliği araştırmalarında ve klinik uygulamalarda önemli bir ölçüt haline gelmiştir. Çocuklarda ve ergenlerde, ağız sağlığına bağlı yaşam kalitesi değerlendirmeleri, benlik algısı, sosyal kabul ve okul ortamı gibi faktörlere dayanarak yetişkinlerden önemli ölçüde farklılık göstermektedir. Bu makalenin amacı, özellikle estetiği etkileyen dental sorunların genç hastalarda sosyal ve duygusal refahı nasıl etkilediğini inceleyerek maloklüzyonlar ve ağız sağlığı ile ilişkili yaşam kalitesi arasındaki ilişkinin genel bir derlemesini sunmaktır. Ayrıca ortodontik tedavinin sosyal ve duygusal açıdan ağız sağlığına bağlı yaşam kalitesini artırmadaki etkinliğini ve hastaya yönelik tedavinin önemini vurgulamaktır. Bu derleme, hastaların fonksiyonel ve duygusal ihtiyaçlarını daha iyi karşılamak ve genel yaşam kalitelerini artırmak için ağız sağlığı ile ilgili yaşam kalitesi ölçeklerinin klinik kararlara entegre edilmesini önermektedir.

Anahtar kelimeler: Ağız sağlığı, yaşam kalitesi, çocuk sağlığı

Cite as: Agani Sabah G, Kanmaz MG. Impact of Orthodontic Treatment on the Oral Health-related Quality of Life in Children. J Behcet Uz Child Hosp. 2024;14(3):127-134

INTRODUCTION

Health-related quality of life (HRQoL) was first defined by the World Health Organization in 1948 as not only the absence of disease but also as a state of physical, mental, and social well-being[1]. It reflects an individual's evaluation of how pain, physical ability, mental health, and social interactions impact his/her own overall well-being[2]. HRQoL started to receive attention in the field of dentistry only in the 1980s and was formally introduced as the "oral HRQoL" (OHRQoL) by Locker in 1988[3]. OHRQoL is defined as a standard health status measurement of oral tissues that contributes to overall well-being by enabling individuals to eat, communicate, and socialize without discomfort or distress[4]. It also emphasizes the positive sense of dentofacial self-confidence, and absence of negative impacts of oral conditions on social life[5].

OHRQoL is a multifactorial construct designed to assess the impact of oral health on an individual's life by capturing subjective experiences across various domains,

including oral health, functional and emotional well-being. By using OHRQoL measures, treatment outcomes benefiting individual patients can be better defined[6].

Measures of OHRQoL in Children

Patient perceptions are crucial in assessing overall need, particularly in OHRQoL, which is highly age-dependent, leading to notable differences in OHRQoL between children and adults[7,8]. While adult OHRQoL tools have been available for decades, instruments tailored specifically for children and adolescents have emerged more recently, allowing researchers to explore OHRQoL factors specific to younger populations, such as self-image, social acceptance, and the school environment (Table 1)[9].

Among these tools, the Child Perceptions Questionnaire (CPQ)[10,11] and the Child Oral Health Impact Profile (COHIP)[12] have become the most widely used approaches for assessing OHRQoL in preadolescent[13].

The CPQ was the first instrument designed specifically to evaluate OHRQoL in children[22]. It comes in two versions tailored to different age groups-one for children aged 8 to 10 and another for those aged 11 to 14 years. The CPQ assesses OHRQoL across four key domains: oral symptoms, functional limitations, emotional well-being, and social well-being[10,11]. While the emotional well-being subscale addresses internal feelings, such as worries, embarrassment, or concerns regarding physical appearance, the social well-being

Table 1. Measures of OHRQoL in children

Measures of OHRQoL	Abbreviation	Year published	Age range	Domains	Number of items	Informant (child/proxy)
Child Perceptions Questionnaire[10]	CPQ_{8-10}	2004	8-10	- Oral symptoms - Functional limitations - Emotional well- being - Social well- being	25	Child
Child Perceptions Questionnaire[11]	CPQ_{11-14}	2002	11-14	- Oral symptoms - Functional limitations - Emotional well- being - Social well- being	37	Child
Child Oral Health Impact Profile[12]	COHIP	2007	7-18	- Oral health - Functional well- being - Social/emotional well-being - School environment - Self- image	34	Child
Child Oral Health Impact Profile (Short Form)[14]	COHIP SF	2012	8-17	- Oral health - Functional well- being - Social/emotional well-being - School environment - Self- image	19	Child
Child Oral Health Impact Profile-Ortho[15]	COHIP-ortho	2016	8-13	- Oral health - Functional well- being - Social/emotional well-being - School environment - Self- image	11	Child
Child Oral Health Impact Profile-Preschool version[16]	COHIP-preschool	2017	2-5	- Oral health - Functional well- being - Social/emotional well- being - Self- image	11	Proxy/parent

Table 1. Devamı

Measures of OHRQoL	Abbreviation	Year published	Age range	Domains	Number of items	Informant (child/proxy)
Child-Oral Impacts on Daily Performances Index[17]	C-OIDP	2004	10-12	- Eating - Speaking - Cleaning mouth - Sleeping - Emotion - Smiling - Study - Social contact	8	Child
Scale of Oral Health Outcomes[18]	SOHO-5	2012	5	Not specified	7	Child
Pediatric Oral Health-Related Quality of Life[19]	POQL	2011	2-12	- Social functioning - Role functioning - Physical functioning - Emotional functioning	20	Child proxy/ parent
Parental Caregiver Perceptions Questionnaire[20]	P-CPQ	2003	8-14	- Oral symptoms - Functional limitations - Emotional well- being - Social well- being	31	Proxy/Parent
Early Childhood Oral Health Impact Scale[21]	ECOHIS	2007	3-5	- Child symptoms - Child function - Child psychological - Child self- image/social interaction - Parent distress - Family function	13	Proxy/Parent

OHRQoL: Oral health-related quality of life

subscale includes items that evaluate how oral health affects social interactions, such as participating in class, engaging in social activities, smiling, talking with peers, and feelings of being teased by other children[23]. Each item assesses the frequency of specific events affecting teeth, lips, and jaws over the previous three months with higher scores indicating worse OHRQoL. This measure has demonstrated its validity, reliability, and responsiveness across various settings[24-28].

COHIP on the other hand was designed for use in both research and clinical settings to distinguish between children with different clinical conditions of various levels of severity. Originating from the same initial item pool as the CPQ, the COHIP includes 34 items across five domains: oral health, functional well-being, social and emotional well-being, school environment, and self-image. Participants are asked to rate the frequency of events over the past three months using a scale that includes both positive and negative items. Negative items are reverse-scored, leading to lower scores indicating poorer OHRQoL[12,29,30]. Since COHIP incorporates both positive and negative impacts, it can assess not only the absence of conditions but also enhanced well-being, such as increased self-confidence due to care. A recently validated short form with 19 items further facilitates quick and efficient OHRQoL assessment in clinical studies[14].

Applications of OHRQoL Measures in Pediatric Dentistry

Children are often affected by various dentofacial disorders that impact their physical functioning and psychosocial well-being. Assessing the impact of oral health on their daily lives is essential, as oral diseases can restrict their current physical, social, and psychological well-being. During late childhood or pre-adolescence, children may experience high rates of caries, poor nutritional habits, dental anxiety, eating disorders, and heightened concerns about other people's perceptions

about themselves, all contributing to unique social and psychological needs. Therefore, a deeper understanding of OHRQoL and its impact on dental and clinical factors in children is crucial to delivering optimal oral healthcare and improving their overall oral health[31].

Unlike traditional objective criteria such as decay, missing teeth, and fillings, OHRQoL assessments are a valuable tool in pediatric caries research, since they capture satisfaction, symptom relief, and enhanced functional and emotional well-being. Research consistently shows a modest but significant link between unmet dental needs, such as decay, and children's OHRQoL[6]. Greater numbers of caries and tooth loss are significantly associated with lower OHRQoL, and children experience significant improvements in their OHRQoL after receiving dental treatment[6,32]. Anterior tooth extractions without replacement and untreated fractured anterior teeth are also associated with lower OHRQoL since they have a substantial socio-dental impact on children's daily lives compared to those without traumatic dental injuries[32].

Dental fear in 11-14-year-old patients has been strongly associated with poorer OHRQoL, potentially due to contributing factors such as infrequent dental visits and higher rates of dental caries. Research further highlights links between dental fear and various factors, including pain-related past and recent dental visits, lower family income, lower paternal education, larger family size, previous hospitalizations, and health issues, all of which have been associated with poorer OHRQoL. Conversely, having received a filling during previous dental visits is associated with improved OHRQoL[31]. Additionally, untreated dental caries and dental pain are linked to functional limitations, psychological challenges, and negative impacts on social and emotional well-being[31,33].

Poor periodontal health also results in higher total CPQ 11-14 scores across all domains. Conditions like gingivitis, gingival bleeding, and plaque buildup are likely linked to more profound negative perceptions of oral health and daily life. Gingival bleeding, in particular, influences children's social interactions and self-esteem, while overall unhealthy periodontal conditions negatively influence emotional and social well-being. Severe malocclusion has been linked to plaque accumulation, which can lead to the development of periodontitis[34].

Association Between OHRQoL and Orthodontic Treatment Need

Research on the physical, social, and psychological consequences of malocclusion has highlighted its significant impact on quality of life. Evidence shows that even very young 8-year-old patients, often prioritize the aesthetic and social aspects of OHRQoL when seeking orthodontic treatment. As orthodontic research increasingly adopts a more psychosocial perspective, there is also a growing interest in understanding and improving OHRQoL[35,36]. Orthodontic treatment is usually performed when the permanent dentition begins to emerge, coinciding with the period when children become more aware of their appearance and gain autonomy to request or refuse treatment[37]. Children with unaesthetic dental traits and untreated malocclusions often face teasing and negative social responses which may lead to psychological and social challenges, as they begin to experience increased self-awareness about their appearance[35,37,38].

Various malocclusion characteristics, such as an increased overjet, spaced dentition[38-41], and maxillary anterior crowding of 2 mm or more[42], have been linked to negative impacts on OHRQoL. Studies have shown that these malocclusions predominantly affect emotional and social well-being[37,40], with noticeable negative effects recorded as early as the age of eight[41]. Early orthodontic treatment is often recommended to protect the children from negative impacts on their OHRQoL, with potential benefits such as improved self-esteem and fewer negative social interactions[40,43]. Both children and parents commonly believe that orthodontic treatment can improve dental function, aesthetic dental appearance, and overall quality of life. The advantages of orthodontic treatment depend on the severity of the malocclusion and the child's perception of the issue[44].

Although malocclusion is not a disease but rather a deviation from societal aesthetic norms, there has been a demand for its orthodontic care for decades, driven largely by self-perceived dental appearance[45]. To objectively assess the need for treatment, various indices have been developed[46-49], with the Index of Orthodontic Treatment Need (IOTN)[50] being one of the most widely used indices due to its practical and efficient application. The IOTN evaluates the necessity for treatment through two components: the Dental Health Component, which assesses oral health factors, and the Aesthetic Component, which considers aesthetic impairments.

Orthodontic treatment is often sought not only for functional concerns but also to relieve the aesthetic impact of malocclusion, which can affect quality of life[44]. Traditionally, assessments of orthodontic needs have focused less on a patient's perspective about his/her malocclusion and more on how treatment can improve their daily lives. However, there is a growing

understanding that measuring OHRQoL should be central to clinical practice[39]. Orthodontic treatment need indices have limitations, as they fail to address how malocclusion affects quality of life, particularly in terms of functional limitations and psychological well-being[51]. Additionally, these tools may be insensitive to individual concerns and overlook minor irregularities that could matter deeply to the patient. There is also a risk of treating patients without a genuine psychosocial need, leading to potential over-treatment[51].

Over the past decade, focusing on patient-centered aspects of orthodontic treatment has gained greater momentum in medicine and dentistry. Understanding the need for orthodontic treatment from both the patient's and clinician's perspectives improves treatment planning and contributes to heightened quality of life. Research has shown that, for many patients, the appearance of their teeth and facial aesthetics is a more compelling reason for seeking orthodontic care than functional concerns. The need for orthodontic treatment can, therefore, stem from either the orthodontist's (normative) perspective or the patient's (subjective) viewpoint, or both[52].

Efforts to link OHRQoL with clinical orthodontic indicators have often yielded mixed results. Although numerous studies have demonstrated a significant relationship between the need for orthodontic treatment and OHRQoL[25,39,44,51-56], findings suggest that malocclusion itself has a negative impact, more deeply on emotional well-being[45,51] than on function or social domains[57]. Children with untreated malocclusions who desired orthodontic treatment reported significantly poorer OHRQoL[51] and the severity of malocclusion was found to be closely related to poorer OHRQoL[55]. Studies indicate that a child's psychological profile plays a significant role in shaping the social and emotional effects of malocclusion. Specifically, low self-esteem in children significantly impacts quality of life due to malocclusion, suggesting self-esteem is a more influential factor than the severity of malocclusion in determining orthodontic treatment need[45,58]. Studies examining ethnic, gender, and age differences in OHRQoL expectations have also found that young patients are more motivated by improved dental aesthetics or appearance than by improvements in oral function[36]. OHRQoL has been found to be poorer in girls while boys were more affected by functional restrictions[59,60].

However, some studies did not find a significant correlation between the requirement for orthodontic treatment and OHRQoL[61,62], and children with severe malocclusions were not always those who reported poorer OHRQoL[51,63]. This fact could be attributed to and might be explained by the possibility that some children with severe malocclusions exhibit greater resilience to the challenges posed by their condition[23]. Also, low self-reported OHRQoL did not necessarily indicate a stronger desire for treatment[51]. Consequently, precise interpretation of OHRQoL measures necessitates comprehension of their psychometric characteristics and the contextual elements that may affect assessments of health and well-being in these patients[23].

Impact of Orthodontic Treatment on OHRQoL

Studies using reliable OHRQoL measures have highlighted notable differences between orthodontic patients who have and have not undergone treatment[24,64], particularly in terms of socioemotional aspects like smiling, laughing, and displaying teeth without feeling self-conscious[36]. Studies have shown that children and adolescents who received orthodontic treatment experienced significant improvements in their OHRQoL compared to untreated peers matched for age, sex, and dental condition[23]. Adolescents who underwent two years of fixed orthodontic treatment reported particularly noticeable benefits in their emotional and social well-being. However, these positive effects were less evident in the oral function and functional limitations domains[65-67].

A longitudinal study tracking 197 adolescents during the first six months of fixed-appliance therapy observed an improvement in their CPQ domains, despite anticipated challenges and children's expectations of functional, emotional, and social problems to be experienced during treatment[68]. Additionally, a twenty-year observational study revealed that individuals with severe malocclusion, aged eleven to twelve years at baseline, who underwent orthodontic treatment during adolescence, reported greater satisfaction with their dental and general appearance. A superior quality of life was noted in comparison to untreated individuals with substantial treatment needs, underscoring the long-term advantages of orthodontic treatment[69].

Some studies suggest that the psychological benefits of orthodontic treatment may be less pronounced than commonly assumed. Analyses of the CPQ_{11-14} subscales reveal that the impact of treatment varies across four domains, with significant effects observed only in emotional well-being. In contrast, orthodontic treatment

does not immediately improve children's social well-being, possibly because it takes time for children to translate the emotional benefits of treatment into social contexts[23].

Moreover, the results of orthodontic treatment appear to be influenced by the interplay between psychological factors and the perceived social and emotional effects of dental health[42,70,71]. It seems that children exhibiting higher psychological well-being tend to report better OHRQoL, irrespective of their orthodontic treatment status. On the other hand, children with low psychological well-being who did not undergo orthodontic treatment reported worse OHRQoL compared to their treated counterparts. This may suggest that orthodontic treatment may be advantageous for children with lower psychological well-being[23]. Many studies have examined the effect of orthodontic treatment on self-esteem. Nonetheless, there is no definitive proof that orthodontic therapy improves self-esteem[36,38,69,72], as it has been shown to be a reasonably stable psychological construct[73]; hence, minimal or no impact of orthodontic treatment on self-esteem is expected[36,38,69,72].

CONCLUSION

OHRQoL has emerged as a critical measure in dentistry, highlighting the comprehensive impact of oral health on individuals' physical, emotional, and social well-being. The growing body of research underscores the importance of OHRQoL assessments, particularly in children and adolescents, as they reflect not only physical and functional health but also self-perception and social interactions. The association between malocclusion and OHRQoL is well-documented, with evidence pointing to its significant psychosocial and unfavorable impacts, such as teasing and reduced self-confidence.

This review highlights the importance of orthodontic treatment in improving OHRQoL, especially in the domains of emotional and social well-being. While some children experience notable psychological and social benefits after treatment, others may show limited improvements, suggesting that individual psychological factors play a key role in perceived treatment outcomes. This complexity highlights the need for a holistic, patient-centered approach in orthodontic care, where clinicians consider both objective clinical measures and the subjective experiences of patients.

Ethics

Author Contributions

Concept: G.A.S., M.G.K., Design: G.A.S., M.G.K., Literature Search: G.A.S., M.G.K., Writing: G.A.S., M.G.K.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Testa MA, Simonson DC. Assessment of quality-of-life outcomes. N Engl J Med. 1996;334(13):835-40. doi: 10.1056/NEJM199603283341306
2. WHOQoL Group. Study protocol for the World Health Organization project to develop a Quality of Life assessment instrument (WHOQOL). Qual Life Res. (2):153-9. doi: 10.1007/bf00435734
3. Locker D. Measuring oral health. A conceptual framework. Community Dent Health. 1988;5(1):3-18.
4. Locker D. Does dental care improve the oral health of older adults?. Community Dent Health. 2001;18(1):7-15.
5. Inglehart MR. Oral health-related quality of life. Quintessence Pub. 2002.
6. Genderson MW, Sischo L, Markowitz K, Fine D, Broder HL. An overview of children's oral health-related quality of life assessment: from scale development to measuring outcomes. Caries Res. 2013;47(Suppl 1):13-21. doi: 10.1159/000351693
7. John MT, Hujoel P, Miglioretti DL, LeResche L, Koepsell TD, Micheelis W. Dimensions of oral-health-related quality of life. J Dent Res. 2004;83(12):956-60. doi: 10.1177/154405910408301213
8. Tapsoba H, Deschamps JP, Leclercq MH. Factor analytic study of two questionnaires measuring oral health-related quality of life among children and adults in New Zealand, Germany and Poland. Qual Life Res. 2000;9(5):559-69. doi: 10.1023/A:1008931301032
9. Wilson-Genderson M, Broder HL, Phillips C. Concordance between caregiver and child reports of children's oral health-related quality of life. Community Dent Oral Epidemiol. 2007;35(Suppl 1):32-40. doi: 10.1111/j.1600-0528.2007.00403.x
10. Jokovic A, Locker D, Tompson B, Guyatt GJ. Questionnaire for measuring oral health-related quality of life in eight-to ten-year-old children. Pediatr. Dent. 2004;26(6):512-8.
11. Jokovic A, Locker D, Stephens M, Kenny D, Tompson B, Guyatt GJ. Validity and reliability of a questionnaire for measuring child oral-health-related quality of life. J Dent Res. 2002;81(7):459-63. doi: 10.1177/154405910208100
12. Broder HL, Wilson-Genderson M. Reliability and convergent and discriminant validity of the Child Oral Health Impact Profile (COHIP Child's version). Community Dent Oral Epidemiol. 2007;35(Suppl 1):20-31. doi: 10.1111/j.1600-0528.2007.0002.x
13. Thomson WM, Broder HL. Oral-health-related quality of life in children and adolescents. Pediatr Clin North Am. 2018;65(5):1073-84. doi: 10.1016/j.pcl.2018.05.015
14. Broder HL, Wilson-Genderson M, Sischo L. Reliability and validity testing for the child oral health impact profile-reduced (COHIP-

SF 19). J Public Health Dent. 2012;72(4):302-12. doi: 10.1111/j.1752-7325.2012.00338.x

15. Kragt L, Tiemeier H, Wolvius EB, Ongkosuwito EM. Measuring oral health-related quality of life in orthodontic patients with a short version of the child oral health impact profile (COHIP). J Public Health Dent. 2016;76(2):105-12 doi: 10.1111/jphd.12118
16. Ruff RR, Sischo L, Chinn CH, Broder HL. Development and validation of the child oral health impact profile-preschool version. Community Dent Health. 2017;34(3):176-82. doi: 10.1922/CDH_4110Ruff07
17. Gherunpong S, Tsakos G, Sheiham A. Developing and evaluating an oral health-related quality of life index for children; the CHILD-OIDP. Community Dent Health. 2004;21(2):161-9.
18. Tsakos G, Blair YI, Yusuf H, Wright W, Watt RG, Macpherson LM. Developing a new self-reported scale of oral health outcomes for 5-year-old children (SOHO-5). Health Qual Life Outcomes. 2012;10:1-8. doi: 0.1186/1477-7525-10-62
19. Huntington NL, Spetter D, Jones JA, Rich SE, Garcia RI, Spiro III A. Development and validation of a measure of pediatric oral health-related quality of life: the POQL. J Public Health Dent. 2011;71(3):185-93. doi: 10.1111/j.1752-7325.2011.00247.x
20. Jokovic A, Locker D, Stephens M, Kenny D, Tompson B, Guyatt G. Measuring parental perceptions of child oral health-related quality of life. J Public Health Dent. 2003;63(2):67-72. doi: 10.1111/j.1752-7325.2003.tb03477.x
21. Pahel BT, Rozier RG, Slade GD. Parental perceptions of children's oral health: the Early Childhood Oral Health Impact Scale (ECOHIS). Health Qual Life Outcomes. 2007;5:6. doi: 10.1186/1477-7525-5-6
22. Locker D, Jokovic A, Tompson B. Health-related quality of life of children aged 11 to 14 years with orofacial conditions. Cleft Palate Craniofac J. 2005;42(3):260-6 doi: 10.1597/03-077.1
23. Agou S, Locker D, Muirhead V, Tompson B, Streiner DL. Does psychological well-being influence oral-health-related quality of life reports in children receiving orthodontic treatment?. Am J Orthod Dentofacial Orthop. 2011;139(3):369-77 doi: 10.1016/j.ajodo.2009.05.034
24. O'Brien K, Wright JL, Conboy F, Macfarlane T, Mandall N. The child perception questionnaire is valid for malocclusions in the United Kingdom. Am J Orthod Dentofacial Orthop. 2006;129(4):536-40. doi: 10.1016/j.ajodo.2004.10.014
25. Foster Page LA, Thomson WM, Jokovic A, Locker D. Validation of the child perceptions questionnaire (CPQ11-14). J Dent. Res. 2005;84(7):649-52. doi: 10.1177/154405910508400713
26. Locker D, Jokovic A, Tompson B, Prakash P. Is the Child Perceptions Questionnaire for 11-14 year olds sensitive to clinical and self-perceived variations in orthodontic status? Community Dent Oral Epidemiol. 2007;35(3):179-85. doi: 10.1111/j.1600-0528.2006.00324.x
27. Agou S, Malhotra M, Tompson B, Prakash P, Locker D. Is the child oral health quality of life questionnaire sensitive to change in the context of orthodontic treatment? A brief communication. J Public Health Dent. 2008;68(4):246-8. doi: 10.1111/j.1752-7325.2008.00093.x
28. Do LG, Spencer AJ. Evaluation of oral health-related quality of life questionnaires in a general child population. Community Dent Health. 2008;25(4):205-10.
29. Dunlow N, Phillips C, Broder HL. Concurrent validity of the COHIP. Community Dent Oral Epidemiol. 2007;35(Suppl 1):41-9. doi: 10.1111/j.1600-0528.2007.00404.x
30. Ravaghi V, Mokhatry Ardakan MM, Shahriari S, Mokhtari N, Underwood M. Comparison of the COHIP and OHIP-14 as measures of the oral health-related quality of life of adolescents. Community Dent Health. 2011;28(1):82-8.
31. Merdad L, El-Housseiny AA. Do children's previous dental experience and fear affect their perceived oral health-related quality of life (OHRQoL)?. BMC Oral Health. 2017;17(1):47. doi: 10.1186/s12903-017-0338-9
32. Omara M, Stamm T, Bekes K. Four-dimensional oral health-related quality of life impact in children: a systematic review. J Oral Rehabil. 2021;48(3):293-304. doi: 10.1111/joor.13066
33. Barasuol JC, Santos PS, Moccelini BS, Magno MB, Bolan M, Martins-Júnior PA, et al. Association between dental pain and oral health-related quality of life in children and adolescents: A systematic review and meta-analysis. Community Dent Oral Epidemiol. 2020;48(4):257-63. doi: 10.1111/cdoe.12535
34. De Stefani A, Bruno G, Irlandese G, Barone M, Costa G, Gracco A. Oral health-related quality of life in children using the child perception questionnaire CPQ11-14: a review. Eur Arch Paediatr Dent. 2019;20:(5):425-30. doi: 10.1007/s40368-019-00418-8
35. Cunningham SJ, Hunt NP. Quality of life and its importance in orthodontics. J Orthod. 2001;28(2):152-8. doi: 10.1093/ortho.28.2.152
36. Kiyak HA. Does orthodontic treatment affect patients' quality of life? J Dent Educ. 2008;72(8):886-94.
37. Dimberg L, Arnrup K, Bondemark L. The impact of malocclusion on the quality of life among children and adolescents: a systematic review of quantitative studies. Eur J Orthod. 2015;37(3):238-47. doi: 10.1093/ejo/cju046
38. DiBiase AT, Sandler PJ. Malocclusion, orthodontics and bullying. Dental Update. 2001;28(9):464-6. doi: 10.12968/denu.2001.28.9.464
39. Johal A, Cheung MY, Marcene W. The impact of two different malocclusion traits on quality of life. Br Dent J. 2007;202(2):E2. doi: 10.1038/bdj.2007.33
40. Kallunki J, Sollenius O, Paulsson L, Petrén S, Dimberg L, Bondemark L. Oral health-related quality of life among children with excessive overjet or unilateral posterior crossbite with functional shift compared to children with no or mild orthodontic treatment need. Eur J Orthod. 2019;41(2):111-6. doi: 10.1093/ejo/cjy033
41. Sardenberg F, Martins MT, Bendo CB, Pordeus IA, Paiva SM, Auad SM, et al. Malocclusion and oral health-related quality of life in Brazilian school children. Angle Orthod. 2013;83(1):83-9. doi: 10.2319/010912-20.1
42. Marques LS, Ramos-Jorge ML, Paiva SM, Pordeus IA. Malocclusion: esthetic impact and quality of life among Brazilian schoolchildren. Am J Orthod Dentofacial Orthop. 2006;129(3):424-7. doi: 10.1016/j.ajodo.2005.11.003
43. O'Brien K, Wright J, Conboy F, Chadwick S, Connolly I, Cook P, et al. Effectiveness of early orthodontic treatment with the Twin-block appliance: a multicenter, randomized, controlled trial. Part 2: Psychosocial effects. Am J Orthod Dentofacial Orthop. 2003;124(5):488-94. doi: 10.1016/j.ajodo.2003.06.001
44. Liu Z, McGrath C, Hägg U. The impact of malocclusion/orthodontic treatment need on the quality of life: a systematic review. Angle Orthod. 2009;79(3):585-91 doi: 10.2319/042108-224.1
45. De Baets E, Lambrechts H, Lemiere J, Diya L, Willems G. Impact of self-esteem on the relationship between orthodontic treatment need and oral health-related quality of life in 11-

to 16-year-old children. Eur J Orthod. 2012;34(6):731-7. doi: 10.1093/ejo/cjr088

46. Cons NC, Jenny J, Kohout FJ, Songpaisan Y, Jotikastira D. Utility of the dental aesthetic index in industrialized and developing countries. J Public Health Dent. 1989;49(3):163-6. doi: 10.1111/j.1752-7325.1989.tb02054.x
47. Daniels C, Richmond S. The development of the index of complexity, outcome and need (ICON). J Orthod. 2000;27(2):149-62. doi: 10.1093/ortho/27.2.149
48. Richmond S, Shaw WC, O'Brien KD, Buchanan IB, Jones R, Stephens C, et al. The development of the PAR Index (Peer Assessment Rating): reliability and validity. Eur J Orthod. 1992;14(2):125-39. doi: 10.1093/ejo/14.2.125
49. Khandakji MN, Ghafari JG. Evaluation of commonly used occlusal indices in determining orthodontic treatment need. Eur J Orthod. 2020;42(1):107-14. doi: 10.1093/ejo/cjz042
50. Brook PH, Shaw WC. The development of an index of orthodontic treatment priority. Eur J Orthod. 1989;11(3):309-20. doi: 10.1093/oxfordjournals.ejo.a035999
51. Kok YV, Mageson P, Harradine NW, Sprod AJ. Comparing a quality of life measure and the Aesthetic Component of the Index of Orthodontic Treatment Need (IOTN) in assessing orthodontic treatment need and concern. J Orthod. 2004;31(4):312-8. doi: 10.1179/14653120422502062
52. Theodoridou MZ, Heraclides A, Lamnisos D. Need for orthodontic treatment and oral health-related quality of life in children and adolescents-A systematic review. Community Dent Health. 2024;41(1):5-13. doi: 10.1922/CDH_00125Theodoridou09
53. Paula JS, Leite IC, Almeida AB, Ambrosano GM, Pereira AC, Mialhe FL. The influence of oral health conditions, socioeconomic status and home environment factors on schoolchildren's self-perception of quality of life. Health Qual Life Outcomes. 2012;10:6. doi: 10.1186/1477-7525-10-6
54. Feu D, de Oliveira BH, de Oliveira Almeida MA, Kiyak HA, Miguel JA. Oral health-related quality of life and orthodontic treatment seeking. Am J Orthod Dentofacial Orthop. 2010;138(2):152-9. doi: 10.1016/j.ajodo.2008.09.033
55. Scapini A, Feldens CA, Ardenghi TM, Kramer PF. Malocclusion impacts adolescents' oral health–related quality of life. Angle Orthod. 2013;83(3):512-8. doi: 10.2319/062012-509.1
56. Foster Page LA, Thomson WM, Ukra A, Baker SR. Clinical status in adolescents: is its impact on oral health-related quality of life influenced by psychological characteristics?. Eur J Oral Sci. 2013;121(3 Pt 1):182-7. doi: 10.1111/eos.12034
57. Spalj S, Slaj M, Varga S, Strujic M, Slaj M. Perception of orthodontic treatment need in children and adolescents. Eur J Orthod. 2010;32(4):387-94. doi: 10.1093/ejo/cjp101
58. Agou S, Locker D, Streiner DL, Tompson B. Impact of self-esteem on the oral-health-related quality of life of children with malocclusion. Am J Orthod Dentofacial Orthop. 2008;134(4):484-9. doi: 10.1016/j.ajodo.2006.11.021
59. Ashari A, Mohamed AM. Relationship of the Dental Aesthetic Index to the oral health-related quality of life. Angle Orthod. 2016;86(2):337-42. doi: 10.2319/121014-896.1
60. Ghijselings I, Brosens V, Willems G, Fieuws S, Clijmans M, Lemiere J. Normative and self-perceived orthodontic treatment need in 11-to 16-year-old children. Eur J Orthod. 2014;36(2):179-85. doi: 10.1093/ejo/cjt042
61. Marshman Z, Rodd H, Stern M, Mitchell C, Locker D, Jokovic A, et al. An evaluation of the Child Perceptions Questionnaire in the UK. Community Dent Health. 2005;22(3):151-5.
62. Dimberg L, Lennartsson B, Bondemark L, Arnrup K. Oral health-related quality-of-life among children in Swedish dental care: the impact from malocclusions or orthodontic treatment need. Acta Odontol Scand. 2016;74(2):127-33. doi: 10.3109/00016357.2015.1059485
63. Birkeland K, Bøe OE, Wisth PJ. Orthodontic concern among 11-year-old children and their parents compared with orthodontic treatment need assessed by index of orthodontic treatment need. Am J Orthod Dentofacial Orthop. 1996;110(2):197-205. doi: 10.1016/S0889-5406(96)70109-9
64. Zhang M, McGrath C, Hägg U. Changes in oral health-related quality of life during fixed orthodontic appliance therapy. Am J Orthod Dentofacial Orthop. 2008;133(1):25-9. doi: 10.1016/j.ajodo.2007.01.024
65. Andiappan M, Gao W, Bernabe E, Kandala NB, Donaldson AN. Malocclusion, orthodontic treatment, and the Oral Health Impact Profile (OHIP-14): Systematic review and meta-analysis. Angle Orthod. 2015;85(3):493-500. doi: 10.2319/051414-348.1
66. Feu D, Miguel JA, Celeste RK, Oliveira BH. Effect of orthodontic treatment on oral health–related quality of life. Angle Orthod. 2013;83(5):892-8. doi: 10.2319/100412-781.1
67. O'Brien C, Benson PE, Marshman Z. Evaluation of a quality of life measure for children with malocclusion. J Orthod. 2007;34(3):185-93. doi: 10.1179/146531207225022185
68. Zhang M, McGrath C, Hägg U. Patients' expectations and experiences of fixed orthodontic appliance therapy: impact on quality of life. Angle Orthod. 2007;77(2):318-22. doi: 10.2319/0003-3219(2007)077[0318:PEAEOF]2.0.CO;2
69. Shaw WC, Richmond S, Kenealy PM, Kingdon A, Worthington H. A 20-year cohort study of health gain from orthodontic treatment: psychological outcome. Am J Orthod Dentofacial Orthop. 2007;132(2):146-57. doi: 10.1016/j.ajodo.2007.04.009
70. Kressin NR, Reisine S, Spiro III A, Jones JA. Is negative affectivity associated with oral quality of life?. Community Dent Oral Epidemiol. 2001;29(6):412-23. doi: 10.1034/j.1600-0528.2001.290602.x
71. Klages U, Bruckner A, Zentner A. Dental aesthetics, self-awareness, and oral health-related quality of life in young adults. Eur J Orthod. 2004;26(5):507-14. doi: 10.1093/ejo/26.5.507
72. Birkeland K, Bøe OE, Wisth PJ. Relationship between occlusion and satisfaction with dental appearance in orthodontically treated and untreated groups. A longitudinal study. Eur J Orthod. 2000;22(5):509-18. doi: 10.1093/ejo/22.5.509
73. Huang C. Mean-level change in self-esteem from childhood through adulthood: Meta-analysis of longitudinal studies. Rev Gen Psychol. 2010;14(3):251-60. doi: 10.1037/a0020543

DOI: 10.4274/jbuch.galenos.2024.96992
J Dr Behcet Uz Child Hosp 2024;14(3):135-140

Original Article

Speech and Language Delay in Children: Child Neurology Experience

Çocuklarda Konuşma ve Dil Gecikmesi: Çocuk Nörolojisi Deneyimi

Betül Diler Durgut, Emine Tekin

Giresun University Faculty of Medicine, Department of Pediatrics, Division of Pediatric Neurology, Giresun, Turkey

ABSTRACT

Objective: Speech delay in early childhood can signify various underlying issues, including neurological disorders. The study aims to comprehensively investigate the etiology of speech delay in children aged 2-5 years and to delineate potential neurological disorders associated with this condition.

Method: A total of 220 patients presenting with speech delay/disorder between 2018 and 2021 were included in the study. Data obtained detailed analysis of medical history, physical examinations, developmental assessments, brain magnetic resonance imaging scans, electroencephalography recordings, chromosome karyotype analysis and array comparative genomic hybridization, Brainstem Evoked Response Audiometry were retrospectively reviewed, and recorded retrospectively on pre-prepared data forms.

Results: Majority (80%) of the study cohort had isolated language delay, while 20% had global developmental delay (GDD). Autism emerged as the most frequently diagnosed condition among children with GDD, followed by other significant diagnoses including neurofibromatosis, cerebral palsy, intellectual disability, hypothyroidism, and Rett syndrome.

Conclusion: These results underscore the significance of neurological evaluation in children presenting with speech delay, as it serves as a pivotal step in identifying potential developmental issues early on, such as ASD or GDD. This study contributes valuable insights into understanding the multifaceted nature of speech delay in early childhood and highlights the importance of assuming a holistic approach towards assessment and intervention in affected children.

Keywords: Speech delay, autism, global developmental disorders

ÖZ

Amaç: Erken çocukluk döneminde konuşma gecikmesi, nörolojik bozukluklar da dahil olmak üzere altta yatan çeşitli sorunlara işaret edebilir. Çalışma, 2-5 yaş arası çocuklarda konuşma gecikmesinin etiyolojisini kapsamlı bir şekilde araştırmayı ve bu durumla ilişkili potansiyel nörolojik bozuklukları tanımlamayı amaçlamaktadır.

Yöntem: Çalışmaya 2018 ve 2021 yılları arasında konuşma geriliği/gecikmesi/bozukluğu ile başvuran toplam 220 hasta dahil edildi. Tıbbi geçmiş incelemeleri, fiziksel muayene bulguları, gelişimsel değerlendirmeler, beyin manyetik rezonans görüntüleme taramaları, elektroensefalografi kayıtları, kromozom karyotip analizi ve array tabanlı karşılaştırmalı genomik hibridizasyon (dizi "comparative genomic hybridization"), İşitsel Beyin Sapı Davranımı Testi verileri önceden hazırlanmış veri formlarına retrospektif olarak kaydedildi.

Bulgular: Katılımcı grubunun %80'inde izole dil gecikmesi, %20'sinde ise global gelişimsel gecikme olduğu saptandı. Otizm, global gelişimsel gecikme yaşayan çocuklar arasında en sık teşhis edilen durumdu ve diğer önemli teşhisler arasında nörofibromatoz, serebral palsi, zeka geriliği, hipotiroidizm ve Rett sendromu yer aldı.

Sonuç: Bu sonuçlar, konuşma gecikmesi/geriliği ile başvuran çocuklarda nörolojik değerlendirmenin öneminin altını çizmektedir; çünkü bu, otizm spektrum bozukluğu veya genel gelişimsel gecikme gibi potansiyel gelişimsel sorunların erken dönemde belirlenmesinde önemli bir adım olarak hizmet etmektedir. Bu çalışma, erken çocukluk döneminde konuşma gecikmesinin çok yönlü doğasının anlaşılmasına yönelik değerli bilgiler sunmakta ve etkilenen çocuklarda değerlendirme ve müdahaleye yönelik bütünsel bir yaklaşımın önemini vurgulamaktadır.

Anahtar kelimeler: Konuşma gecikmesi, otizm, global gelişimsel bozukluklar

Received: 08.07.2024
Accepted: 16.08.2024

Corresponding Author
Betül Diler Durgut,
Giresun University Faculty of Medicine, Department of Pediatrics, Division of Pediatric Neurology, Giresun, Turkey
betuldlr@hotmail.com
ORCID: 0000-0002-0322-2843

Cite as: Diler Durgut B, Tekin E. Speech and Language Delay in Children: Child Neurology Experience. J Behcet Uz Child Hosp. 2024;14(3):135-140

INTRODUCTION

Speech and language skills play a crucial role in child development, and deficiencies in these areas are referred to as communication disorders. These disorders are common neurodevelopmental conditions of childhood, classified by the "Diagnostic and Statistical Manual of Mental Disorders-V" (DSM-V) into categories including language disorder, speech sound disorder, childhood-onset fluency disorder (stuttering), social (pragmatic) communication disorder, and unspecified communication disorder[1].

According to DSM-V criteria, to establish the diagnosis of language or speech sound disorder, the condition must not be attributable to general health status, neurological disorders, or general developmental delay[2]. Thus, a thorough neurological evaluation in patients with speech and language disorders is essential to identify any potential underlying or concomitant neurological conditions, such as epilepsy or cerebral palsy (CP).

Speech delay refers to a delay in achieving language development milestones and it is one of the most common complaints among individuals with speech and language disorders. While the prevalence of speech delay is around 10-15% among 2-year-old and drops to approximately 4-5% after the age of three[3,4].

The aim of this study is to investigate the etiology of speech delay in the 2-5 year age group and to shed light on possible underlying neurological disorders.

MATERIALS and METHODS

Children aged 2-5 years who presented to the pediatric neurology outpatient clinic between 2018 and 2021 with complaints of speech delay, or disorder were enrolled in the study. Detailed medical histories, physical examination findings, developmental assessments, brain magnetic resonance imaging (MRI) scan, electroencephalography (EEG), chromosome karyotype analysis, vitamin B12 and hemoglobin test results of the patients were retrospectively reviewed.

The patients were evaluated to determine whether they had isolated language impairment or global developmental delay (GDD) using the Denver Developmental Screening Test (DDST). DDST is a tool used to screen developmental delays in children aged 0-6 years. It evaluates children in four domains: motor skills, language development, social skills, and personal-social development. Patients who are delayed only in the language domain compared to their peers are considered to have an isolated language delay, while those who are delayed in multiple developmental domains (motor, language, social, cognitive) compared to their peers are considered to have GDD. In our study, isolated language delay was defined as a delay only in the language domain of the DDST. Since patients with a delay in the language domain were included in the study, GDD was defined as a delay in at least one additional domain (motor, social, or cognitive) along with the language domain.

In case of need auditory evaluation was conducted using the Brainstem Evoked Response Audiometry (BERA) test.

For each patient presenting with speech delay, screen time was inquired and appropriate recommendations were provided.

The diagnosis of Attention-Deficit/Hyperactivity Disorder (ADHD) was taken into consideration for patients monitored by child psychiatry under this diagnosis.

Children who exhibited normal receptive language skills and had undergone a normal diagnostic work-up but displayed clear expressive language delay were categorized as "late talkers".

Statistical Analysis

Statistical analysis of data was performed using the Statistical Package for the Social Sciences version 25 (SPSS 25.0) software, and results were presented as numbers and percentages. The descriptive statistics of the quantitative variables that conformed to the normal distribution were shown as mean ± standard deviation, and the descriptive statistics of the quantitative variables that were not normally distributed were shown as median (minimum-maximum) or mean ± standard deviation.

Ethical approval was obtained from the Clinical Research Ethics Committee of the University of Health Sciences Turkey, Kanuni Sultan Süleyman Training and Research Hospital (approval number: 2022/05, date: 01.10.2022).

RESULTS

A total of 220 patients who presented to the pediatric neurology outpatient clinic with complaints of speech delay or disorder were included in the study. Study population consisted of 46 (20.9%) female and 174 (79.1%) male patients. Family history of speech delay

was revealed in 34.1% of the patients, and 1.4%. of them was bilingual. The characteristics of the patients are detailed in Table 1. EEGs were performed for 86 (39%) patients. EEG results were abnormal in 5.1% of the patients (Table 2). Two patients were diagnosed with concomitant epilepsy. Cranial imaging was performed for 31 patients, revealing periventricular leukomalacia, hydrocephalus, a cerebellar mass, and an arachnoid cyst in one patient each. BERA test performed on 29 patients oculd not detect hearing loss in patients. In 5 patients, chromosome karyotype analysis and array comparative genomic hybridization were performed; and, single-gene analysis carried out in one patient established the diagnosis of Rett syndrome.

Table 1. Characteristic features of the patients

Personal and family history	n (%)
Prematurity	33 (15)
Neonatal intensive care hospitalization	46 (20.9)
Phototherapy	18 (8.2)
Febrile seizure	8 (3.1%)
Afebrile seizure	3 (1.4%)
Speech delay in family	75 (34.1%)
Consanguinity	21 (9.5%)
Bilingualism	3 (1.4%)

Table 2. EEG findings

EEG findings (n=86)	n (%)
Normal	77 (35)
Background activity disorganisation	1 (0.5)
Interictal epileptiform activity	8 (4.6)

EEG: Electroencephalography

Table 3. Etiologic factors and accompanying diagnoses

Etiologic factors and accompanying diagnoses		n	% (~)
Isolated language disorder (n=176/220)	Late talkers	62	28.1
	Fluency disorder-stuttering	19	8.6
	Other isolated language disorder	95	43.1
	ADHD*	4*	
	Epilepsy*	1*	
GDD (n=44/220)	Autism	19	8.6
	Mental retardation	2	1
	NF-1	2	1
	Cerebral palsy	1	0.5
	Hypothyroidism	1	0.5
	Rett syndrome	1	0.5
	Undiagnosed patients	18	8.1
	Epilepsy*	1*	
	ADHD*	2*	
	Cerebellar mass*	1*	

*Accompanying diagnosis, ADHD: Attention-deficit/hyperactivity disorder, NF-1: Neurofibromatosis Type 1, GDD: Global developmental delay

Mean hemoglobin value was 12.4±0.88 g/dL and median B12 value was 368 pg/mL (104-2000). Three patients had iron deficiency anemia, and four patients had vitamin B12 deficiency.

Isolated language disorder was diagnosed in 176 (80%) patients, while GDD was identified in 44 (20%) patients. In patients with GDD, autism was the most frequently identified etiology (8.6%). The etiology GDD could not be determined in 8.1% of the patients. The etiologic factors and accompanying diagnoses are summarized in Table 3. The patients with isolated language delay, had also asthma (n=3), had atrial septal defect (n=1) and ventricular septal defect (n=1). Incidentally, a cerebellar mass was detected in one patient with GDD.

DISCUSSION

In our study, we have demonstrated that 20% of patients presenting solely with complaints related to speech delay were diagnosed with GDD. Therefore, patients with speech delay should be thoroughly examined. A multitude of etiologies can contribute to childhood speech and language delay. In children presenting with speech and language retardation, a comprehensive developmental assessment is essential, as atypical language development may serve as the first indicator of other physical and developmental issues[5].

Many studies have reported that the ratio of affected males to females in specific language disorder is approximately 2:1 to 3:1[6,7]. Consistent with the literature, in our study there was a male gender predominance with a ratio of 3.8:1 (79.1%)[5,8]. Additionally, conditions associated with language delay, such as GDD/intellectual disability and autism spectrum disorder (ASD), are more common in males rather than females[9-11].

Some authors have reported an increased incidence of language-related disorders among family members of children with language disorders, with a range of 28% to 50%[12-14]. In the present study, a positive family history was revealed in our 75 (34.1%) patients.

Isolated Language Delay

For early recognition of speech delay, it is crucial to have a good understanding of the developmental process. Red flags for speech delay include not using the words mama/papa/dada to call parents at 12 months, not having learnt at least 5 words at 18 months, and using less than 50 words and not being able to connect two words at 24 months of age. In our study, the final diagnoses of patients who presented with complaints of speech delay and were diagnosed with isolated language delay are outlined in Table 3. Among patients with isolated speech delay, 62 out of 176 (28.1%) were identified as late talkers. Late talkers typically have a significantly lower word count compared to their peers at the age of 24 months. However, half of these children catch up with normal speech milestones by the age of 3 years[15,16]. Since we lack data on the final language development status of all patients, we cannot make a comment on this issue.

One of the important diagnoses that should not be overlooked in patients presenting with speech delay is hearing loss. In our study, although hearing loss was not detected in any patient with were identified, we observed that hearing test could be applied at a low rate which may be attributed to patients' poor compliance with the tests and the families' adherence to the diagnostic procedures.

Stuttering can be classified as developmental, neurogenic, or psychogenic. Neurological stuttering is rare and typically follows a neurological event such as acquired brain damage, brain injury, or stroke[17,18]. In the present study, 19 children were diagnosed with stuttering, and none of them had neurogenic stuttering.

Early detection of patients with isolated language delay and initiation of appropriate therapy are crucial for prognosis. Furthermore, delays in language development may serve as early signs of more common problems such as ASD, GDD, and intellectual disability[19,20].

Global Developmental Delay

GDD is defined as a delay in two or more developmental domains, including gross/fine motor skills, speech/language, and personal/social communication skills, affecting children under the age of 5 years[21]. Common etiologies of GDD include genetic syndromes/chromosomal abnormalities, intrapartum asphyxia, cerebral dysgenesis, psychosocial deprivation, metabolic diseases, neurocutaneous diseases, intrauterine infections, hypothyroidism, and toxin exposure[22-24]. Additionally, GDD can occur in combination with behavioral problems such as ASD and attention-deficit hyperactivity disorder[25].

In our study, GDD was observed in 44 out of 220 (20%) patients, and etiologic factors were identified in twenty-six of them. Etiologic factors could not be determined in 18 (40.9%) cases. The most prevalent diagnosis was autism, identified in 19 patients. Other identified diagnoses included mental retardation, Neurofibromatosis Type 1, CP, hypothyroidism, and Rett syndrome (Table 3). In Ozmen et al.[26], investigated 247 patients with GDD, and reported perinatal complications in 21%, chromosomal abnormalities in 9%, genetics/dysmorphic syndromes in 3%, metabolic disorders in 4%, hypothyroidism in 4%, neurocutaneous syndromes in 3%, intrauterine infection in 2%, and disorders of unknown etiology in 36% of their cases. GDD has a wide variety of etiologies. In our study, the low proportion of patients with identified etiology and limited diversity is due to our inclusion criteria, which only encompassed patients with complaints of speech delay. The presentation of patients with conditions related to asphyxia/perinatal complications, chromosomal abnormalities, genetics/dysmorphic syndromes, and metabolic disorders would have different, irrelevant complaints. Zengin-Akkuş et al.[20] found non-autistic developmental delay in 15%, autism in 16%, isolated speech delay in 50%, and normal language development in 19% of patients presenting to the developmental pediatric outpatient clinic with speech delay[20]. Unlike our study, the rate of isolated speech delay was lower in their study[20]. This difference could be attributed to the inclusion of patients with normal language development in their study.

The overall etiologic yield in an unselected series of children under 5 years of age with GDD is close to 40% and 55% in the absence of any concomitant autistic features[23]. These rates may vary according to the study method and design, as well as the severity of GDD. Consistent with the literature, the etiologic factors could be determined in 59% (26/44) of patients with GDD[24].

Shan et al.[27] analyzed clinical data of 521 children with GDD aged between 24 and 60 months. The prevalence of ASD in children with GDD was 62.3%[27], whereas this rate was 43.2% (19/44) in our study. The high rates of autism highlight the importance of autism screening in patients presenting with language disorder and GDD. Children with autism often experience delays in speech/language and personal/social developmental domains. Additionally, some patients may also exhibit delays in gross/fine motor domains.

Perinatal asphyxia is commonly associated with developmental delay[23,26]. In our study, we observed only one patient diagnosed with CP. We attributed detection of scarce number of CP cases to the presentation of these patients to the outpatient clinic predominantly with motor retardation before language delay becomes apparent.

The history of agnosia should be investigated in patients presenting with a language disorder because language comprehension (auditory verbal agnosia) and verbal expression loss (aphasia) are characteristic diagnostic features of Landau-Kleffner syndrome (LKS). LKS is a rare childhood disorder, and most of these patients exhibit severe EEG abnormalities during sleep. However, there were no patients diagnosed with Landau-Kleffner syndrome in the present study.

EEG recordings provide valuable information within specific clinical contexts such as Angelman syndrome, Wolf-Hirschhorn syndrome, as well as in cases of agnosia/aphasia or a clinical history of seizure/epilepsy[28]. In our study, EEGs were performed in 86 out of 220 patients, and two of these patients with a history of seizures were diagnosed with epilepsy. However, we did not identify any specific EEG patterns for particular clinical conditions. In larger series, specific EEG findings may be detected.

In acquired language disorders, patients should be evaluated for potential neurodevelopmental and neurodegenerative diseases such as Leigh encephalopathy, Rett syndrome, metachromatic leukodystrophy, and mucopolysaccharidoses. Other considerations include middle ear infections, neglect/abuse, and head trauma. In the current study, one patient with acquired language disorder was diagnosed with Rett syndrome. Rett syndrome is characterized by stereotypical hand movements, gait abnormalities, loss of speech and purposeful hand use, and normal early development. It is well known that Rett syndrome occurs in females, and acquired microcephaly is its significant clinical characteristics. Mutation analysis of the *MECP2* gene should be ordered in patients exhibiting characteristic symptomatology.

Mental retardation, learning disability, ADHD, and pervasive developmental disorder (autism spectrum) are conditions commonly associated with language disorders in children and adolescents[29]. Research has shown that 30.4% of children in the speech-language impaired (SD/LI) group had ADHD based on the DSM-III (1980) criteria, compared to 4.5% of controls[30]. In our study, six patients had coexisting ADHD. The lower rate observed in our study may be attributed to the retrospective nature of the study and the relatively young age range of our patient group.

Language disorders commonly occur as a symptom of ASD and GDD. Therefore, developmental assessment tools such as the DDST, along with diagnostic tools like MRI, EEG, genetic, and metabolic screening tests, should be considered for patients whose language disorders cannot be diagnosed through detailed history and physical examination[24,27,31,32].

CONCLUSION

In conclusion, it's important to emphasize the possibility of secondary neurological and behavioral problems in patients presenting with speech/language delay. It should also be kept in mind that neurodevelopmental disorders like ADHD may be accompanied by comorbid conditions. In the medical history, particular attention should be given to the perinatal process, and neurological clues such as microcephaly, dysmorphic features, hypotonia, verbal agnosia/aphasia, and skin findings should be thoroughly investigated during physical examination.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Clinical Research Ethics Committee of the University of Health Sciences Turkey, Kanuni Sultan Süleyman Training and Research Hospital (approval number: 2022/05, date: 01.10.2022).

Informed Consent: Retrospective study.

Author Contributions

Surgical and Medical Practices: B.D.D., E.T., Concept: B.D.D., E.T., Design: B.D.D., E.T., Data Collection and Processing: B.D.D., E.T., Analysis and Interpretation: B.D.D., Literature Search: B.D.D., Writing: B.D.D., E.T.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. American Psychiatric Association. Diagnostic and statical manual of mental disorders. 5th ed. Washington, DC: American Psychiatric Association; 2013.
2. Mukaddes NM, Ercan ES, Nörogelişimsel Bozukluklar; İstanbul, Nobel Tıp Kitabevi. 2018.

3. Stein MT, Parker S, Coplan J, Feldman H. Expressive language delay in a toddler. J Dev Behav Pediatr. 2001;22(2 Suppl):S99-103. https://pubmed.ncbi.nlm.nih.gov/11332819/
4. Collisson BA, Graham SA, Preston JL, Rose MS, McDonald S, Tough S. Risk and Protective Factors for Late Talking: An Epidemiologic Investigation. J Pediatr. 2016;172:168-74.e1. doi: 10.1016/j.jpeds.2016.02.020
5. Chaimay B, Thinkhamrop B, Thinkhamrop J. Risk factors associated with language development problems in childhood-a literature review. J Med Assoc Thai. 2006;89(7):1080-6. Erratum in: Clin Pediatr (Phila). 2017;56(10):979. doi: 10.1177/0009922817720961
6. Bishop DV. Pre-and perinatal hazards and family background in children with specific language impairments: a study of twins. Brain Lang. 1997;56(1):1-26. doi: 10.1006/brln.1997.1729
7. Lahey M, Edwards J. Specific language impairment: preliminary investigation of factors associated with family history and with patterns of language performance. J Speech Hear Res. 1995;38(3):643-57. doi: 10.1044/jshr.3803.643
8. Korpilahti P, Kaljonen A, Jansson-Verkasalo E. Identification of biological and environmental risk factors for language delay: The let's talk STEPS study. Infant Behav Dev. 2016;42:27-35. doi: 10.1016/j.infbeh.2015.08.008
9. Yeargin-Allsopp M, Rice C, Karapurkar T, Doernberg N, Boyle C, Murphy C. Prevalence of autism in a US metropolitan area. JAMA. 2003;289(1):49-55. doi: 10.1001/jama.289.1.49
10. Yeargin-Allsopp M, Drews CD, Decouflé P, Murphy CC. Mild mental retardation in black and white children in metropolitan Atlanta: a case-control study. Am J Public Health. 1995;85(3):324-8. doi: 10.2105/ajph.85.3.324
11. Bertrand J, Mars A, Boyle C, Bove F, Yeargin-Allsopp M, Decoufle P. Prevalence of autism in a United States population: the Brick Township, New Jersey, investigation. Pediatrics. 2001;108(5):1155-61. doi: 10.1542/peds.108.5.1155
12. Campbell TF, Dollaghan CA, Rockette HE, Paradise JL, Feldman HM, Shriberg LD, et al. Risk factors for speech delay of unknown origin in 3-year-old children. Child Dev. 2003;74(2):346-57. doi: 10.1111/1467-8624.7402002
13. Robinson RJ. Causes and associations of severe and persistent specific speech and language disorders in children. Developmental Medicine & Child Neurology. 1991;33:943-62. doi: 10.1111/j.1469-8749.1991.tb14811.
14. Neils J, Aram DM. Family history of children with developmental language disorders. Percept Mot Skills. 1986;63(2 Pt 1):655-8. doi: 10.2466/pms.1986.63.2.655
15. Roos EM, Weismer SE. Language outcomes of late talking toddlers at preschool and beyond. Perspect Lang Learn Educ. 2008;15(3):119-26. doi: 10.1044/lle15.3.119
16. Rescorla L, Dahlsgaard K, Roberts J. Late-talking toddlers: MLU and IPSyn outcomes at 3;0 and 4;0. J Child Lang. 2000;27(3):643-64. doi: 10.1017/s0305000900004232
17. Grant AC, Biousse V, Cook AA, Newman NJ. Stroke-associated stuttering. Arch Neurol. 1999;56(5):624-7. doi: 10.1001/archneur.56.5.624
18. Rose SC, Weldy DL, Zhukivska S, Pommering TL. Acquired stuttering after pediatric concussion. Acta Neurol Belg. 2022;122(2):545-6. doi: 10.1007/s13760-021-01653-x
19. Mody M, Belliveau JW. Speech and Language Impairments in Autism: Insights from Behavior and Neuroimaging. N Am J Med Sci (Boston). 2013;5(3):157-61. doi: 10.7156/v5i3p157
20. Zengin-Akkuş P, Çelen-Yoldaş T, Kurtipek G, Özmert EN. Speech delay in toddlers: Are they only "late talkers"? Turk J Pediatr. 2018;60(2):165-72. doi: 10.24953/turkjped.2018.02.008
21. Shevell M, Ashwal S, Donley D, Flint J, Gingold M, Hirtz D, et al. Practice parameter: evaluation of the child with global developmental delay: report of the Quality Standards Subcommittee of the American Academy of Neurology and The Practice Committee of the Child Neurology Society. Neurology. 2003;60(3):367-80. doi: 10.1212/01.wnl.0000031431.81555.16
22. Shevell MI, Majnemer A, Rosenbaum P, Abrahamowicz M. Etiologic yield of subspecialists' evaluation of young children with global developmental delay. J Pediatr. 2000;136(5):593-8. doi: 10.1067/mpd.2000.104817
23. Srour M, Mazer B, Shevell MI. Analysis of clinical features predicting etiologic yield in the assessment of global developmental delay. Pediatrics. 2006;118(1):139-45. doi: 10.1542/peds.2005-2702
24. Bélanger SA, Caron J. Evaluation of the child with global developmental delay and intellectual disability. Paediatr Child Health. 2018;23(6):403-19. doi: 10.1093/pch/pxy093
25. Boyle J. Speech and language delays in preschool children. BMJ. 2011;343:d5181. doi: 10.1136/bmj.d5181
26. Ozmen M, Tatli B, Aydinli N, Calişkan M, Demirkol M, Kayserili H. Etiologic evaluation in 247 children with global developmental delay at Istanbul, Turkey. J Trop Pediatr. 2005;51(5):310-3. doi: 10.1093/tropej/fmi023
27. Shan L, Feng JY, Wang TT, Xu ZD, Jia FY. Prevalence and Developmental Profiles of Autism Spectrum Disorders in Children With Global Developmental Delay. Front Psychiatry. 2022;12:794238. doi: 10.3389/fpsyt.2021.794238
28. Battaglia A, Bianchini E, Carey JC. Diagnostic yield of the comprehensive assessment of developmental delay/mental retardation in an institute of child neuropsychiatry. Am J Med Genet. 1999;82(1):60-6. https://pubmed.ncbi.nlm.nih.gov/9916845/
29. Carter J. Etiology of speech and language disorders in children up to date. Last updated: 2022;Nov 30 https://pro.uptodatefree.ir/show/616 accessed 14 Dec 2022
30. Beitchman JH, Nair R, Clegg M, Ferguson B, Patel PG. Prevalence of psychiatric disorders in children with speech and language disorders. J Am Acad Child Psychiatry. 1986;25(4):528-35. doi: 10.1016/s0002-7138(10)60013-1
31. Srivastava S, Love-Nichols JA, Dies KA, Ledbetter DH, Martin CL, Chung WK, et al. Meta-analysis and multidisciplinary consensus statement: exome sequencing is a first-tier clinical diagnostic test for individuals with neurodevelopmental disorders. Genet Med. 2019;21(11):2413-21. doi: 10.1038/s41436-019-0554-6
32. Moeschler JB, Shevell M; Committee on Genetics. Comprehensive evaluation of the child with intellectual disability or global developmental delays. Pediatrics. 2014;134(3):e903-18. doi: 10.1542/peds.2014-1839.

DOI: 10.4274/jbuch.galenos.2024.24022
J Dr Behcet Uz Child Hosp 2024;14(3):141-145

Original Article

Correlation of the Interval Between Single Phase Computed Tomography and Direct Abdominal Radiography with the Success of Collecting System Imaging in Trauma Patients

Travma Hastalarında Tek Fazlı Bilgisayarlı Tomografi ve Direkt Batın Grafisi Arasındaki Sürenin Toplayıcı Sistem Görüntüleme Başarısı ile İlişkisi

Bade Toker Kurtmen[1], Bengisu Karbuzoğlu[1], Sibel Tiryaki[2]

[1]University of Health Sciences Turkey, İzmir Tepecik Training and Research Hospital, Clinic of Pediatric Surgery, İzmir, Turkey
[2]University of Health Sciences Turkey, İzmir Tepecik Training and Research Hospital, Clinic of Pediatric Urology, İzmir, Turkey

ABSTRACT

Objective: A triple-phase computed tomography (CT) is required to visualize post-traumatic ureteral injury in children. An abdominal X-ray following single-phase contrast enhanced CT is performed both to evaluate urinary tract and to reduce the radiation exposure in our center. The aim of this study was to designate an optimal interval between CT and X-ray in imaging the urinary collecting system.

Method: Records of pediatric trauma patients who underwent a CT scan were analyzed. CT and X-ray images were evaluated and the time interval between two imaging modalities was calculated. The success of X-ray in demonstrating bilateral renal pelvises, ureters and bladder was evaluated.

Results: The study population consisted of 190 patients with a male predominance (72.6%) and a median age of 9 years (2 months-17.9 years). The median time interval between the CT and X-ray was 59.5 minutes. Time interval between both imaging modalities was significantly longer if the images were not satifactorily demonstrative (72.5 vs. 39.5 minutes) (p<0.001). Age (p=0.722), gender (p=0.203) and type of trauma (p=0.796) had no effect on this time interval. When the patients were grouped according to the time elapsed between these two imaging modalities as 10-30 minutes (Group 1) and longer (Group 2), the proportion of patients with optimally demonstrative X-rays was significantly higher in Group 1 (p=0.001).

Conclusion: Ureter injuries are rare and cannot be mostly diagnosed with single-phase CT-scans, but a triple-phase scan increases the radiation burden especially for children. Our plan is to validate our technique using an X-ray following CT-scan for evaluating the urinary tract in trauma, and this preliminary retrospective study confirmed that time interval of 10-30 minutes between these two imaging modalities should be considered in future studies.

Keywords: Trauma, injuries, tomography, X-ray, children, ureter

ÖZ

Amaç: Çocuklarda travma sonrası üreter hasarını görüntülemek için 3 fazlı bilgisayarlı tomografi (BT) gereklidir. Merkezimizde radyasyon maruziyetini azaltmak için üriner sistemi değerlendirmek için tek fazlı BT'yi takiben bir abdominal röntgen çekilmektedir. Bu çalışmanın amacı, üriner toplayıcı sistemin görüntülenmesinde BT ve röntgen arasındaki optimal süreyi belirlemektir.

Yöntem: BT taraması yapılan pediatrik travma hastalarının kayıtları analiz edildi. BT ve röntgen görüntüleri değerlendirildi ve iki modalite arasındaki süre hesaplandı. X-ışınının bilateral renal pelvisleri, üreterleri ve mesaneyi görüntülemedeki başarısı değerlendirildi.

Bulgular: Erkek ağırlıklı (%72,6) ve ortanca yaşı 9 yıl (2 ay-17,9 yıl) olan 190 hasta vardı. BT ve röntgen arasındaki ortalama süre 59,5 dakika idi. Süre, başarısız görüntülerde (72,5 dakika) başarılı olanlara (39,5 dakika) göre anlamlı olarak daha uzundu (p<0,001). Yaş (p=0,722), cinsiyet (p=0,203) ve travma tipinin (p=0,796) etkisi yoktu. Hastalar süreye göre 10-30 dakika arası (Grup 1) ve diğerleri (Grup 2) olarak gruplandırıldığında, Grup 1'de optimal röntgen çekilen hasta oranı anlamlı olarak daha yüksekti (p=0,001).

Sonuç: Üreter yaralanmaları nadirdir ve çoğunlukla tek fazlı BT taramaları ile tanınamamaktadır. Üç fazlı BT ise özellikle çocuklar için radyasyon yükünü artırır. Planımız, travma sonrası üriner sistem değerlendirilmesi için tek fazlı BT'yi takiben çekilen röntgen ile uyguladığımız tekniğimizi geliştirmektir. Bu ön retrospektif çalışma, gelecekteki çalışmalar için 10-30 dakikanın uygun bir zamanlama olduğunu doğrulamıştır.

Anahtar kelimeler: Travma, yaralanmalar, tomografi, X-ışını, çocuklar, üreter

Received: 13.09.2023
Accepted: 30.08.2024

Corresponding Author
Bade Toker Kurtmen,
University of Health Sciences Turkey, İzmir Tepecik Training and Research Hospital, Clinic of Pediatric Surgery, İzmir, Turkey
badetoker@gmail.com
ORCID: 0000-0001-8963-5755

Cite as: Toker Kurtmen B, Karbuzoğlu B, Tiryaki S. Correlation of the Interval Between Single Phase Computed Tomography and Direct Abdominal Radiography with the Success of Collecting System Imaging in Trauma Patients. J Behcet Uz Child Hosp. 2024;14(3):141-145

INTRODUCTION

Kidneys are the most commonly injured organ of the urinary system in children[1]. Children have a higher risk of renal injury than adults because of lesser perirenal fat, smaller abdominal muscles, and lack of ossification of the rib cage[2]. Ureteral injuries are rare, accounting for only 1% of pediatric abdominal traumas[3]. They are most commonly caused by a penetrating injury, but they can also can occur during blunt trauma[4]. Besides its rarity, ureteral injury is a hard to diagnose problem with no pathognomonic sign or a specific symptom[5]. European Association of Urology and American Urological Association guidelines recommend obtaining intermediate and delayed images with intravenous contrast-enhanced abdominal/pelvic computed tomography (CT) for the diagnosis of ureteric injury[6,7].

CT is a part of common practice for pediatric traumas with strong evidence of intra-abdominal injury when they are hemodynamically stabilized.[8] On the other hand, it carries a high burden of radiation exposure; therefore, clinicians try to limit its use according to the ALARA principles. ALARA is the acronym for "As Low as Reasonably Achievable" which means that the radiation dose delivered to the patients should be as low as reasonably achievable while still providing image quality adequate to enable an accurate diagnosis[9,10]. Abdominopelvic CT scans carry a higher risk of developing radiation-associated malignancies when compared to CT scans of other areas, especially in children[11]. The effective doses of CT-scans vary widely depending on the number of phases obtained; the area scanned or the slice thickness. A single CT scan delivers doses in the range of 10-30 millisievert (mSv), however radiation doses that should be delivered in multiple-phase scanning increase up to of 50-200 mSv due to the use of pre-contrast and post-contrast phases[12].

Portal phase CT is mostly sufficient in detecting renal trauma but it can also fail to reveal ureteric injury. An X-ray following single-phase CT is performed to evaluate the urinary tract to reduce radiation exposure in our center. Up to now, the time interval between CT-scan and X-ray was not standardized as there was no determined protocol for the sequential use of these two imaging modalities. Our plan is to validate the use of this technique in evaluating urinary tract in pediatric trauma patients. This pilot study aims to designate a proper time interval between CT and X-ray in visualization of the collecting system using current data before starting prospective studies.

MATERIALS and METHODS

After approval of the University of Health Sciences Turkey, İzmir Tepecik Training and Research Hospital Non-Interventional Clinical Research Ethics Committee (approval number: 2022/09-12, date: 15.09.2022), the medical records of the pediatric trauma patients between January 2021 and 2022 were retrospectively reviewed. Our hospital is the largest trauma center in a city with a population of 4 million people. A single-phase contrast enhanced CT followed by anteroposterior abdominal X-ray routtinely performed in our center. Both to evaluate urinary tract and also to reduce the radiation exposure. All children (<18 years old) who admitted to our hospital and underwent CT were included in the study. Patients with incomplete medical records and who did not undergo X-ray scanning following CT scans were excluded from the study. Informed consent was obtained from the parents/guardians of all children.

Data concerning qualifying demographic features, age at diagnosis, present symptoms, physical examination findings, and type of diagnostic imaging technique performed were retrieved from the hospital records. CT and X-ray images were evaluated and the time interval between two modalities was calculated. The success of X-ray in visualizing renal pelvises, ureters and bladder was evaluated. The X-rays that demonstrated all urinary collecting system (including pelvises, ureters, and bladder) were termed as "Optimal X-rays".

Statistical Analysis

All pre-organized forms were collected, and data were transferred to Excel 2010 (Microsoft, Redmond WA, USA). The homogeneity of variances was checked using Levene's test. Shapiro-Wilk test was used to test the assumption of normality. To compare the differences between the two groups, an independent sample t-test was used when the parametric test prerequisites were fulfilled, and the Mann-Whitney U test when they were not. The statistical significance between frequencies was calculated by the Pearson's chi-squared/Fisher's exact test. Significance was set at $p<0.05$. Data were evaluated using IBM SPSS Statistics 22.0 (IBM Corp., Armonk, NY, USA).

RESULTS

A total of 190 patients met inclusion criteria. The median age was 9 years (2 months-17.9 years) and 72.6% of patients were male. The majority (89%) had blunt trauma. Falls were the most frequent mechanism of injury (n=84, 44.2%). The median time interval between

CT scan and X-rays was 59.5 minutes (interquartile range: 37-97 minutes, and range: 7-775 minutes).

Optimal visualization of pelvises, ureters, and the bladder (optimal X-ray group) was achieved in 38% of all the X-rays taken (Figure 1). None of the patients had urinary tract injury during the study period. One patient who had a normal X-ray underwent an additional delayed CT scan for a high suspicion of ureteral injury which did not reveal any relevant pathology. There was no significant difference between optimal and suboptimal X-ray groups in terms of age, gender, and trauma type (Table 1). Median time interval between these two imaging modalities was found significantly shorter in optimal X-ray group than suboptimal X-ray group. Comparison of optimal and suboptimal X-ray groups is summarized in Table 1.

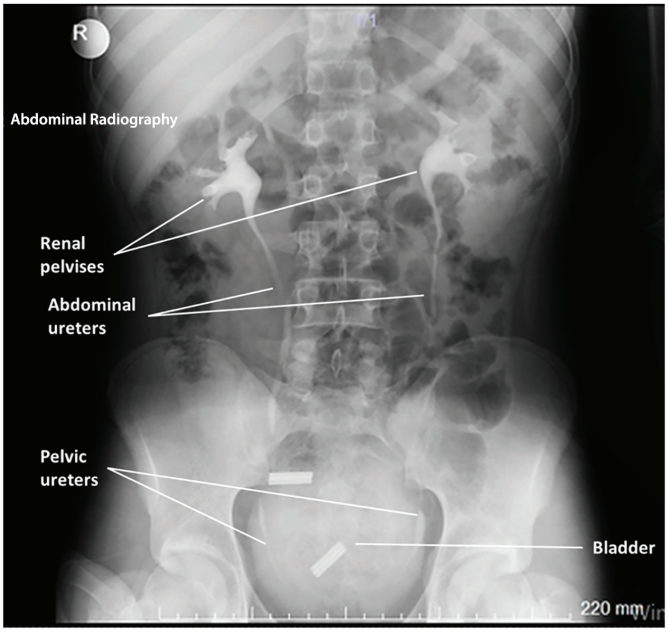

Figure 1. An X-ray of the optimal group obtained approximately 25 minutes after single-phase CT scan

CT: Computed tomography

With the primary objective of identifying a clinically appropriate, and applicable time interval to all trauma patients, we reassessed our data by categorizing the images obtained at 10-minute intervals. We found out that one patient whose X-ray was performed unintentionally within the first ten minutes. No clear image could be obtained in this patient. Bladder could be visualized in at least 90% of the patients in the first hour. However, for ureter and pelvis this rate decreased rapidly if this time interval exceeded half an hour (Figure 2). So, we subgrouped patients according to time intervals in-between as 10-30 minutes (Group 1) or longer (Group 2). There was no significant difference between the two groups in terms of age, gender, and trauma type. The proportion of patients with optimal X-rays was significantly higher in Group 1 (p=0.001). Both ureters and pelvises were visualized optimally in Group 1 (p<0.001 and p=0.011 respectively), while visualization rates of bladders did not differ significantly between both groups (p=0.437). Comparison of subgroups is summarized in Table 2.

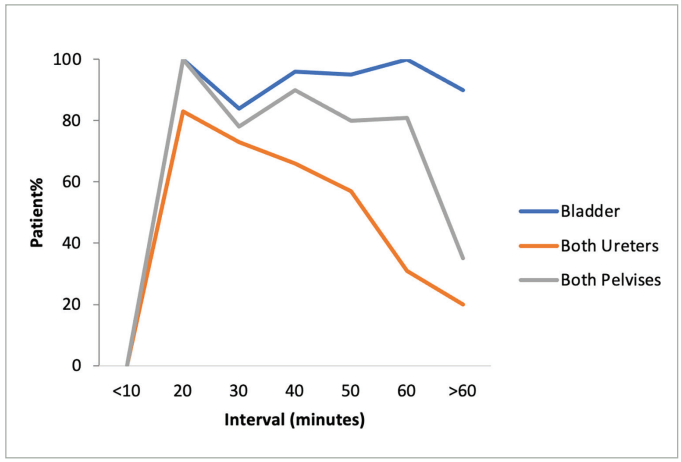

Figure 2. Percentages of patients with imaged bladder (blue), ureters (red) or pelvises (green) on the X-rays performed following CT-scans, grouped according to time intervals between these two imaging modalities

CT: Computed tomography

Table 1. Comparison of optimal and non-optimal X-ray groups (n=190)

	Optimal X-ray group (n=72)	Non-optimal X-ray group (n=118)	p-values
Median age: years (Q1-Q3)	9.3 (5-15)	8.8 (5-15)	0.722[a]
Gender distribution: male; n (%)	48 (67%)	90 (76%)	0.203[b]
Type of trauma exposed: blunt trauma; n (%)	60 (89.8%)	106 (87.5%)	0.796[b]
Median interval time elapse: minutes (Q1-Q3)	39.5 (31-60)	72.5 (47-112)	<0.001[a]

[a]Mann-Whitney U test, [b]Yates' continuity correction test, Q1-Q3: First and third quartiles

Table 2. Comparison of subgroups (n=190)			
	X-rays obtained 10-30 minutes following CT-scans (n=26)	Others (n=164)	p-values
[d]Median age: years (Q1-Q3)	9.0 (5-15)	9.0 (5-14)	0.726[a]
Gender distribution: male: n (%)	20 (77%)	118 (72%)	0.771[b]
Type of trauma exposed: blunt trauma; n (%)	24 (92%)	145 (88%)	0.744[c]
Success of imaging both ureters; n (%)	20 (77%)	57 (35%)	<0.001[b]
Success of imaging both pelvises; n (%)	22 (85%)	92 (56%)	0.011[b]
Success of imaging bladder; n (%)	23 (89%)	152 (93%)	0.437[c]
[a]Mann-Whitney U test, [b]Yates' Continuity correction test, [c]Fisher's exact test, [d]Q1-Q3: First and third quartiles			

DISCUSSION

Trauma is the most common cause of mortality and morbidity in children. Approximately 25% of pediatric trauma patients had abdominal injury and genitourinary tract injury occurs in 10% of the cases with abdominal trauma[7,13-15]. Ureteral trauma is uncommon, accounting for less than 1% of all urologic traumas[16]. Although genitourinary tract trauma in children accounts for 10% of all abdominal trauma, there are not many studies in the literature on the most appropriate imaging modalities to be used in children. Especially visualization of ureters is more problematic. Because ureters cannot be visualized appropriately unless triple-phase CT is performed. Use of this imaging modality increases radiation exposure. There are no studies on how detailed demonstration of ureters can be performed with lower radiation exposure.

In our literature search, we found a few studies on the imaging of genitourinary tract injuries in children. All these studies have referenced research studies performed in adults and recommended intravenous contrast-enhanced CT with a delayed excretory phase[17-19]. Although CT scans are sensitive in detecting ureteral injuries; they come with the significant drawback of high radiation exposure. However, the literature does not provide any recommendations for reducing radiation exposure in these patients.

At our clinic, we employ a cutting-edge technique to visualize the urinary system, and use radiography following a single-phase CT scan. Despite its widespread use in our practice, this method is not supported by existing literature. Therefore, in this study, our goal is to determine the optimal time interval between X-ray and single-phase CT. However, we are planning a prospective study to assess the diagnostic sensitivity and specificity of this technique.

The rarity of ureteral injuries made us question the necessity of triphasic CT scan in pediatric trauma patients. Therefore, we prefer single phase (portal venous) tomography to reduce the radiation exposure in the evaluation of trauma patients and reserve delayed phase CT imaging only for patients with a highly suspected ureteral injury. Instead of a delayed phase CT scan, we routinely perform an X-ray following CT to evaluate the urinary tract. Since we obtained similar image similar to intravenous pyelography in some patients (Figure 1), we aimed to constitute a standardized protocol and validate our technique in diagnosing ureteral injury. This preliminary study was performed to determine an optimal time interval for this protocol, and we found an approximately 38% success rate in visualizing the complete urinary tract and 41% success rate in visualizing both ureters regardless of the time interval elapsed between two scans. Also, as expected, the median time interval between two scans was significantly shorter in optimal X-rays than suboptimal ones. Diagnostic success rates of X-ray was statistically significantly reduced in those taken 60 minutes after CT-scans. The urinary tract as a whole could be visualized in 65% and both ureters in 77% of patients when the X-rays were performed between 10 to 30 minutes after CT scans.

Study Limitations

The major limitation of this study is retrospectively collected data and unstandardized imaging protocol with varying time intervals between these two radiological techniques, but this study provided us the information that predetermined time intervals between two imaging techniques should be between 10 to 30 minutes in future studies. Obtaining this data will allow us to constitute a standardized protocol and our current plan is a prospective study to reveal the diagnostic sensitivity and specificity of this technique.

CONCLUSION

Ureteral disruption is an exceptional injury following trauma in children. Guidelines recommend multi-phase

CT scans to diagnose ureteral injuries, but ALARA principles advise us to reduce radiation exposure especially in children. Our preliminary study showed that an image which provides sufficient anatomic detail to visualize the collecting system could be obtained if an X-ray is performed 10-30 minutes following CT scan. We think this can guide future studies and help constitute a standardized protocol to image urinary tract in trauma patients.

Ethics

Ethics Committee Approval: After approval of the University of Health Sciences Turkey, İzmir Tepecik Training and Research Hospital Non-Interventional Clinical Research Ethics Committee (approval number: 2022/09-12, date: 15.09.2022), the medical records of the pediatric trauma patients between January 2021 and 2022 were retrospectively reviewed.

Informed Consent: Informed consent was obtained from the parents/guardians of all children.

Author Contributions

Surgical and Medical Practices: B.T.K., B.K., S.T., Concept: S.T., Design: B.T.K., S.T., Data Collection and Processing: B.K., Analysis and Interpretation: B.T.K., S.T., Literature Search: B.T.K., Writing: B.T.K.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Grimsby GM, Voelzke B, Hotaling J, Sorensen MD, Koyle M, Jacobs MA. Demographics of pediatric renal trauma. J Urol. 2014;192(5):1498-502. doi: 10.1016/j.juro.2014.05.103
2. Brown SL, Elder JS, Spirnak JP. Are pediatric patients more susceptible to major renal injury from blunt trauma? A comparative study. J Urol. 1998;160(1):138-40. https://pubmed.ncbi.nlm.nih.gov/9628634/
3. Bryk DJ, Zhao LC. Guideline of guidelines: a review of urological trauma guidelines. BJU Int. 2016;117(2):226-34. doi: 10.1111/bju.13040
4. Coccolini F, Moore EE, Kluger Y, Biffl W, Leppaniemi A, Matsumura Y, et al. Kidney and uro-trauma: WSES-AAST guidelines. World J Emerg Surg. 2019;14:54. doi: 10.1186/s13017-019-0274-x
5. Pereira BM, Ogilvie MP, Gomez-Rodriguez JC, Ryan ML, Peña D, Marttos AC, et al. A review of ureteral injuries after external trauma. Scand J Trauma Resusc Emerg Med. 2010;18:6. doi: 10.1186/1757-7241-18-6
6. Kitrey ND, Djakovic N, Hallscheidt P, et al. Urological Trauma. EAU Guidel Eur Assoc Urol. Published online 2016. https://uroweb.org/guideline/urological-trauma/
7. Morey AF, Brandes S, Dugi DD 3rd, Armstrong JH, Breyer BN, Broghammer JA, et al. Urotrauma: AUA guideline. J Urol. 2014;192(2):327-35. doi: 10.1016/j.juro.2014.05.004
8. Basaran A, Ozkan S. Evaluation of intra-abdominal solid organ injuries in children. Acta Biomed. 2019;89(4):505-12. doi: 10.23750/abm.v89i4.5983
9. Joseph BB, George S. The road to radiation safety and ALARA: A review. IP Int J Maxillofac Imaging. 2021;6(4):89-92. doi: 10.18231/j.ijmi.2020.022
10. Uffmann M, Schaefer-Prokop C. Digital radiography: the balance between image quality and required radiation dose. Eur J Radiol. 2009;72(2):202-8. doi: 10.1016/j.ejrad.2009.05.060
11. Miglioretti DL, Johnson E, Williams A, Greenlee RT, Weinmann S, Solberg LI, et al. The use of computed tomography in pediatrics and the associated radiation exposure and estimated cancer risk. JAMA Pediatr. 2013;167(8):700-7. doi: 10.1001/jamapediatrics.2013.311
12. Mettler FA Jr, Wiest PW, Locken JA, Kelsey CA. CT scanning: patterns of use and dose. J Radiol Prot. 2000;20(4):353-9. doi: 10.1088/0952-4746/20/4/301
13. Trinci M, Piccolo CL, Ferrari R, Galluzzo M, Ianniello S, Miele V. Contrast-enhanced ultrasound (CEUS) in pediatric blunt abdominal trauma. J Ultrasound. 2019;22(1):27-40. doi: 10.1007/s40477-018-0346-x
14. Spijkerman R, Bulthuis LCM, Hesselink L, Nijdam TMP, Leenen LPH, de Bruin IGJM. Management of pediatric blunt abdominal trauma in a Dutch level one trauma center. Eur J Trauma Emerg Surg. 2021;47(5):1543-1551. doi: 10.1007/s00068-020-01313-4
15. Nimanya SA, Sekabira J, Kakembo N, Kisa P, Massenga A, Naluyimbazi R, et al. Pediatric abdominal trauma in a National Referral Hospital. Afr Health Sci. 2022;22(Spec Issue):108-13. doi: 10.4314/ahs.v22i2.16S
16. Presti JC Jr, Carroll PR, McAninch JW. Ureteral and renal pelvic injuries from external trauma: diagnosis and management. J Trauma. 1989;29(3):370-4. doi: 10.1097/00005373-198903000-00016
17. Singer G, Arneitz C, Tschauner S, Castellani C, Till H. Trauma in pediatric urology. Semin Pediatr Surg. 2021;30(4):151085. doi: 10.1016/j.sempedsurg.2021.151085
18. Garratt J, Im J, Gupta A, Hill P, Suresh K. Imaging of genitourinary trauma. In: Knollmann F. (eds.) Trauma Computed Tomography. Springer, Cham. https://link.springer.com/chapter/10.1007/978-3-031-45746-3_8
19. Joshi N, Schenker KE, Nikam R, Kandula V. Pediatric Trauma Computed Tomography: A Comprehensive Guide. Trauma Computed Tomography. 2024;255-303. doi: 10.1007/978-3-031-45746-3_12

DOI: 10.4274/jbuch.galenos.2024.79989
J Dr Behcet Uz Child Hosp 2024;14(3):146-152

Original Article

Long-term Outcomes of Patients with Giant Hydronephrosis After Pyeloplasty

Çocukluk Çağı Dev Hidronefroz Olgularının Pyeloplasti Sonrası Uzun Dönem Sonuçları

Ayşe Başak Uçan, Begüm Sönmez, Ayşe Demet Payza, Arzu Şencan

University of Health Sciences Turkey, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital, Clinic of Pediatric Surgery, İzmir, Turkey

ABSTRACT

Objective: The study aims to assess the long-term outcomes of pyeloplasty performed for ureteropelvic junction obstruction (UPJO) with giant hydronephrosis (GH).

Method: Data of 94 patients with ipsilateral UPJO patients who underwent pyeloplasty were analyzed. Patients' demographic characteristics, pre-, and postoperative anteroposterior diameters (APDs) of their kidneys, parenchymal thickness (PT) ratio (PT of ipsilateral/contralateral kidneys) of kidneys, differential renal function (DRF) and surgical outcomes were compared between the GH (group of patients with AP diameter of at least 50 mm as measured on two ultrasonographys with thinner PT than ½ of the contralateral kidney) and the non-GH groups.

Results: Six female, and 18 male children were included in the GH (mean APD: 60.46±9.25 mm), and the remaining 21 female, and 49 male patients in the non-GH group were used as controls. Preoperative PT ratios and DRFs were found to be impaired in the GH group compared to the non-GH group ($p<0,05$). No significant differences were found between the groups in terms of age, gender, laterality of pyeloplasty, operative success. APD and PT ratios of GH and non-GH groups of patients. APD and PT ratios were found to improve significantly after pyeloplasty ($p<0.05$). GH patients who underwent pyeloplasty before 1 year of age experienced significant improvement in their DRFs and PT ratios, while these parameters did not improve in older children who underwent pyeloplasty.

Conclusion: Long-term outcomes of pyeloplasty are satisfactory in pediatric UPJO patients with GH, and their DRFs were stable even in late renograms. Early relief of the obstruction improves PT and renal functions in GH patients younger than 1 year of age.

Keywords: Differential renal function, poorly functioning kidney, pyeloplasty, ureteropelvic junction obstruction, renal parenchymal thickness

ÖZ

Amaç: Çalışmamızın amacı dev hidronefrozu (DH) olan üreteropelvik darlık olgularının (UPD) pyeloplasti sonrası uzun dönem sonuçlarının değerlendirilmesidir.

Yöntem: Kliniğimizde pyeloplasti yapılan toplam 94 (ortalama izlem süresi: 4,8 yıl) tek taraflı UPD hastası analiz edildi. Hastaların demografik özellikleri, ameliyat öncesi ve sonrası ön-arka çap (AP), parankimal kalınlık (PK) oranı (ipsilateral PK/kontralateral PK), diferansiyel böbrek fonksiyonu (DF) analiz edildi ve DH olan ve olmayan gruplar arasında karşılaştırıldı.

Bulgular: DH grubunda (AP çap: 60,46±9,25 mm) 24 (K/E: 6/18) olgu mevcuttu. DH'si olmayan 70 (K/E: 21/49) UPD olgusu kontrol grubu olarak kullanıldı. Ameliyat öncesi DF ve PK oranı DH grubunda DH olmayan gruba göre anlamlı olarak azalmış bulundu ($p<0,05$). Gruplar arasında yaş, cinsiyet, taraf, operatif başarı açısından anlamlı farklılık yoktu. Her iki grupta da hastaların AP çap ve PK oranlarının pyeloplasti sonrası önemli ölçüde düzeldiği görüldü ($p<0,05$). Bir yaştan önce pyeloplasti yapılan DH olgularında DF ve PK oranında anlamlı iyileşme görülürken, 1 yaşından sonra cerrahi uygulanan GH hastalarında anlamlı düzelme saptanmadı ($p<0,05$).

Sonuç: DH olgularında pyeloplasti sonuçları güz güldürücüdür. Özellikle bir yaşın altındaki olgularda obstrüksiyonun ortadan kalkması belirgin bir nefron koruması sağlar.

Anahtar kelimeler: Diferansiyel böbrek fonksiyonu, fonksiyonu bozulmuş böbrek, pyeloplasti, üreteropelvik bileşke darlığı, renal parankimal hasar

Received: 06.05.2024
Accepted: 05.09.2024

Corresponding Author
Ayşe Başak Uçan,
University of Health Sciences Turkey, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital, İzmir, Turkey
abasakucan@yahoo.com
ORCID: 0000-0002-1521-6053

Cite as: Uçan AB, Sönmez B, Payza AD, Şencan A. Long-term Outcomes of Patients with Giant Hydronephrosis After Pyeloplasty. J Behcet Uz Child Hosp. 2024;14(3):146-152

INTRODUCTION

Giant hydronephrosis (GH) is most often defined as the accumulation of more than one liter of fluid in the collecting system or the hydronephrotic kidney crossing the midline or extending more than five vertebral lengths[1,2]. However, these definitions mostly based on adult series are outdated, are not precise or quantitative, and require application of percutaneous nephrostomy or radiological techniques for their confirmation. A few series with a limited number of patients and follow-up intervals have been published in the literature on pediatric patients with GH due to ureteropelvic junction obstruction (UPJO). Most of them have not defined any inclusion criteria for GH in their series[3-5]. Thus there is no consensus on the definition of GH in the pediatric age group.

Our study aims to investigate the long-term outcomes of pyeloplasty in pediatric UPJO patients with GH and proposes a simpler and more practical method for defining GH in the pediatric age group.

MATERIALS and METHODS

Patients with UPJO who underwent dismembered pyeloplasty at our institution from 2008 to 2020 were retrospectively analyzed. Children with bilateral UPJO, solitary kidney or kidney with suprarenal function, as well as those with any other urinary system disorders including vesicoureteral reflux, ureterocele, megaureter, bladder outlet obstruction, and those who have not completed at least one year of follow-up or with missing data, were excluded. Ninety-four patients were divided into GH and non-GH groups according to their parenchymal thickness (PT) ratios, and anteroposterior diameter (APD) of renal pelvises. Patients with an APD of at least 50 mm on two ultrasonographys (USGs) and thinner PT than ½ of the contralateral kidney were included in the GH group. APD measured between the points where the parenchyma ends in the hilus in sections taken in the transverse plane of the kidney by the pediatric radiologist. PT was measured as the minimum distance from the renal capsule to the edge of the renal sinus in the midline sagittal view. APD and PT measured at the last USG before the operation were included in the study as preoperative APD and PT, and one year after the operation as postoperative APD and PT.

Patients' demographic characteristics, preoperative and postoperative APDs, PT ratios (involved side PT/contralateral side PT)[6], differential renal functions (DRFs), and surgical outcomes were compared between groups.

The preoperative and postoperative parameters were compared between groups to clarify the operative benefit. GH patients were also grouped by age (≥1 year of age). Results of DRF, APD, and PT ratios were also compared between both groups.

Negative voiding cystourethrography was seen in all patients. Indications for surgery included impaired split kidney function at and/or a significant obstruction (poor or no response to furosemide) on 99mTc-MAG3 scintigraphy, and impaired PT. Deterioration (≥5%) in renal functions, and an increasing degree of hydronephrosis in successive studies were also considered an indication for operation. Open Anderson-Hynes pyeloplasties were performed on all patients. All GH patients underwent renal pelvic reduction, the extent of which was decided by the surgeons. A double J ureteral stent was inserted in all patients during surgery and removed three weeks later. The success of pyeloplasty was described as gradual improvement of hydronephrosis revealed in postoperative USG and improvement of drainage as detected in MAG3 scintigraphy[7].

Following standard guidelines, DRF was assessed as the percentage of the relative renal activity over the sum of background-corrected total renal activity at 1-2 minutes after the intravascular (IV) injection of radiopharmaceutical agent. Twenty minutes after the injection of a radiopharmaceutical agent, furosemide (1 mg/kg IV) was injected (F+20). Drainage seen on diuretic renogram, starting before or immediately after IV injection of furosemide was termed as Grade 0, delayed drainage after furosemide as Grade 1, and poor or no response to furosemide with a plateau or an upward curve as Grade 2[7]. The 99mTc-MAG3 diuretic renograms were evaluated by the same nuclear physician.

Renal USG was performed one month after the operation, then every 3 months, and yearly thereafter. A 99mTc-MAG3 renogram was performed routinely 6 to 12 months after the operation to confirm operative benefit.

The results of the patients who had undergone renal scintigraphy at postoperative 2-8 years were also compared with the postoperative first year scans to assess whether there was a long-term deterioration in DRF. Unfortunately, since ours was a retrospective study the indications for requesting late-term scintigraphy, which is not used in routine practice could not be fully determined.

Statistical Analysis

The data were analyzed by SPSS V20 software using descriptive (percentage, median, and mean) and analytical statistics (Mann-Whitney U, Wilcoxon Signed Ranks, Pearson's chi-square, and Fisher's exact tests). P<0.05 was considered statistically significant.

Ethical Approval

This study approval by the University of Health Sciences Turkey, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital Clinical Research Ethics Committee (approval number: 2023/09-09-847, date: 22.06.2023). All patients were given information about the procedure, and their consent were obtained.

RESULTS

A total of 94 patients were allocated to GH (6 F/18 M) and non-GH (21 F/49 M) groups according to their APD and PT ratios. The median age of the patients at the time of operation (36.25±51.23 months), the mean APD (60.46±9.25 mm), and the median follow-up period (6.71±3.55 years) were as indicated in the GH group. No significant differences were found in age, gender, laterality of pyeloplasty, and operative success rates between the groups. In the non-GH group, the median age of the patients at the time of operation (30.24±38.33 months) the mean APD (28.55±8.5 mm), and the median follow-up period (4.23±2.89 years) were as indicated (Table 1). Preoperative PT ratios (p<0.001), DRF (p=0.023), and PT (p=0.004) were found to be significantly impaired in the GH group compared to the non-GH group (Table 2). Contrary to DRF, significantly improved postoperative PT ratios, and PT were noted in both groups (Table 2).

Seventeen (70.8%) patients in the GH, and 42 (60%) patients in the non-GH group were younger than 1 year of age. Preoperative DRF was significantly impaired in patients older than one year of age (p=0.024) in the GH group, and PT ratios, and DRFs did not improve after the operation. Contrarily, PT ratios and DRFs significantly improved in patients younger than one year of age (Table 3).

The perioperative and postoperative processes were uneventful for all patients. No anesthesia-related complications were observed in all patients including infants. No patient experienced acute obstruction, urinary leakage, or unexpected readmission.

Reoperation was performed due to a gradual increase in APD in the postoperative period and persistent obstructive drainage pattern (Grade 2) in 99mTc-MAG3 scintigraphy. Reoperation was required in 3 (12.5%), patients in the GH and in 6 (8.6%) patients in the non-GH group. The reoperation rate was not statistically significantly different between groups (p=0.689). One patient in the GH group underwent ureterocalicostomy as a second operation because the ureter was not long enough to perform the ureteropelvic anastomosis.

In the GH group, the preoperative drainage pattern on 99mTc-MAG3 scintigraphy was classified as Grade 2 in 23, and Grade 1 in one patient. In 13 patients, including patients with reoperation, good drainage was observed, and in 8 patients drainage pattern was improved from Grade 2 to 1 in the GH group after the operation. APDs of all patients was also improved in the follow-up visits.

One patient with DRF<10% in the GH group developed hypertension that was controlled by medication after the operation. In the GH group, a second scintigraphy had been performed in 19 patients 2 to 8 years after the operation. Any statistically significant difference was not detected between scintigraphies performed postoperative 1, and also 2-8 years were in terms of DRFs (p=0.944).

Table 1. Comparison of demographics in GH and non-GH group

	GH group	Non-GH group	p-value
Number of the patients	24	70	
Age of the patients (months)	36.25±51.23	30.24±38.33	0.551
Patients <1 year of age	17 (70.8%)	42 (60%)	0.343
Side (R/L)	5/19	21/49	0.386
ANH	19 (79.2%)	50 (71.4%)	0.459
Gender (F/M)	6/18	21/49	0.64
Reoperation	3 (12.5%)	6 (8.6%)	0.689
Follow-up (year)	6.71±3.55	4.23±2.89	0.003

GH: Giant hydronephrosis, R/L: Right/Left, F/M: Female/Male, ANH: Antenatal hydronephrosis

Table 2. Comparison of the preoperative and postoperative DRF, APD, PT and PT ratio in GH group and non-GH group

	GH group	Non-GH group	p-value
DRF			
Preoperative	32.07±14.14	39.13±11.99	0.023
Postoperative	34.83±13.75	39.83±12.99	0.122
p-value	0.057*	0.214**	
APD			
Preoperative	60.46±9.25	28.55±8.5	<0.001
Postoperative	19.48±12.61	11.12±6.14	0.001
p-value	<0.001*	<0.001**	
PT			
Preoperative	3,24±1,46	4.71±2.1	0.004
Postoperative	7,13±2,98	7.31±2.46	0.419
p-value	<0.001*	<0.001**	
PT ratio			
Preoperative	0.33±0.15	0.5±0.2	<0.001
Postoperative	0.65±0.33	0.72±0.22	0.162
p-value	<0.001*	<0.001**	

*Comparison of the preoperative and postoperative DRF, APD, PT and PT ratio in GH group, **Comparison of the preoperative and postoperative DRF, APD, PT and PT ratio in non-GH group. DRF: Differential renal function, APD: Anteroposterior diameter, PT: Parenchymal thickness, GH: Giant hydronephrosis

Table 3. Comparison of preoperative and postoperative DRF, APD, PT and PT ratio in GH group according to age

GH patients according to age, n=24	<1 years of age, n=17	>1 years of age, n=7	p-value
DRF (%)			
Preoperative	36.53±10.78	21.23±16.23	0.024
Postoperative	40.53±10.48	21.00±10.78	0.002
p-value	0.034*	1.000**	
APD (mm)			
Preoperative	60.65±8.1	60±12.37	0.609
Postoperative	16.38±8.12	27±18.46	0.192
p-value	<0.001*	0.028**	
PT (mm)			
Preoperative	3.04±1.21	3.71±1.98	0.260
Postoperative	8.03±2.98	4.93±1.54	0.006
p-value	<0.001*	0.167**	
PT ratio			
Preoperative	0.35±0.15	0.27±0.15	0.374
Postoperative	0.77±0.3	0.34±0.09	0.001
p-value	<0.001*	0.312**	

*Comparison of preoperative and postoperative DRF, APD, PT and PT ratios of patients with <1 year of age, **Comparison of preoperative and postoperative DF, APD, PT and PT ratios of patients with >1 year of age. DRF: Differential renal function, APD: Anteroposterior diameter, PT: Parenchymal thickness, GH: Giant hydronephrosis

DISCUSSION

Data regarding pediatric patients with GH due to UPJO is scarce and there is even no consensus on how to define GH in the pediatric age group[3-5]. In our study, cases with an AP diameter of at least 50 mm on two USGs and with PT thinner than ½ of the contralateral kidney were considered as GH. We thought that overexpansion of the collecting system or the amount of fluid within the collecting system (which might be changed according to the age of the patient) is not sufficient to describe GH in children. Sorrentino defined GH as not only dilatation of the extrarenal or intrarenal pelvis but also the transformation of the kidney into a fluid-filled sac with thin parenchyma[8]. Increased intrarenal pressure reduces renal blood flow and causes glomerular and tubular atrophy and eventually fibrosis[9].

Significant thinning of the renal parenchyma and severe loss of renal function are observed in GH patients. Previous studies have emphasized, but failed to define this decrease in PT[3-4]. The configuration of the renal pelvis may alter the definition of GH. It may be more appropriate to define GH not only as an excessive expansion of the pelvis but its effect on the parenchyma should be also taken into account. Onen's[10]alternative hydronephrosis grading system defines Grade 4 hydronephrosis as severe renal parenchymal loss >1/2 (cyst-like kidney with no visually significant renal parenchyma). We think that a definition that emphasizes the decrease in PT, especially to distinguish the wide extrarenal pelvis from GH, will contribute to an accurate identification of pediatric GH patients. On the other hand, AP diameter of pelvises over 50 mm is defined as gross hydronephrosis by Dhillon and is stated as a definite indication for pyeloplasty[11]. Therefore, it may be a simpler and more practical method to combine these parameters for the pediatric age group and accept cases with an AP diameter of at least 50 mm and a PT thinner than ½ of the opposite kidney as GH.

Our study has confirmed that preoperative PT ratios, DRF, PT were found to be significantly impaired in the GH group compared to the non-GH group (Table 1). In the past years, nephrectomy was preferred in these cases. The incidence of nephrectomy for GH was reported between 3% and 70%[1,12]. Kaura et al.[13] reported in their series, which included both children and adults, that nephrectomy was performed on patients with renal cortical thickness below 5 mm and renal function below 15%. We believe this approach is not suitable for children. It has been shown in pediatric patients that PT and DRF may improve after pyeloplasty[14,15]. Nephrectomy is not recommended anymore even for very poorly functioning kidneys in children[16,17].

Li et al.[15] suggested that compression of the renal parenchyma may be the cause of deterioration in kidney function in some patients and that when the obstruction is relieved, the function of the parenchyma may significantly improve. Yapanoğlu et al.[18] stated that the primary aim of GH treatment is to protect the renal parenchyma. Nerli et al.[5] reported 8 children with GH who underwent laparoscopic pyeloplasty and emphasized improvement in PT in these patients after pyeloplasty. In our series, postoperative improvement of PT was demonstrated in both groups, and improvement in DRF was significant in infants with GH, and PT ratio of GH patients became equal to that of non-GH patients. Moreover, calculating the exact preoperative renal function of a severely dilated kidney is not easy. In this series, nephrectomy was not performed on any of the patients including three cases with poorly functioning (<10%) kidneys in the GH group. PT ratios, and DRFs of all these three patients improved after pyeloplasty. Kim et al.[6] reported that performing pyeloplasty in patients under 1 year of age is an important factor in the recovery of PT. Baek et al.[3] reported that PT increased more in children with GH who underwent surgery under 1 year of age than in children over 1 year of age, and stated that in GH early relief of the obstruction is beneficial[3]. Our study confirmed that, when both groups were examined according to age, PT ratios and DRF improved significantly in patients younger than 1 year of age. Contrary to that, DRF and PT of patients older than 1 year of age were significantly impaired compared to patients younger than 1 year of age and did not improve after pyeloplasty (Table 3). These patients are also susceptible to trauma, which can delay and complicate surgery, therefore they must be diagnosed and operated on as soon as possible.

A severely dilated renal collecting system has difficulty restoring peristalsis and may cause poor renal clearance even after surgery in patients with GH. Nephropexy and nephroplication were suggested so as to improve postoperative drainage patterns[13,19-21]. Kato et al.[19] stated that the postoperative results of those who underwent nephroplication appeared to be better than those who did not. However, this observation was based on a very small number of patients. Shah et al.[22] reported that patients with huge extrarenal pelvis should undergo reduction pyeloplasty combined with nephropexy to reduce stasis and improve drainage by better aligning the pelvicalyceal system with the upper ureter. On the

contrary, in their adult series Sataa et al.[23] stated that such a procedure was not necessary and did not improve renal drainage. Reduction pyeloplasty was performed in this series, but none of the patients underwent nephropexy or nephroplication. It is obvious to expect a decrease in APD of the renal pelvis in patients who underwent pelvis reduction. However, it should not be forgotten that in cases with persistent obstruction and the need for reoperation during follow-up, APD of the renal pelvis increases gradually and is the first suspicious finding for recurrent obstruction. Therefore, we think that the gradual decrease in APD during follow-up, together with the regression of the obstructive pattern in MAG3 scintigraphy, is an important criterion indicating the success of the operation. It has been reported that the best indicators of the relief of obstruction in GH patients are the decrease in APD in USG and the stability of DRF in diuretic renography[3,4]. In our series, significant decrease in APD of renal pelvis was achieved, and postoperative drainage was satisfactory. The long-term preservation of renal function was also demonstrated. This may be related to the fact that all of the patients are in the pediatric age group and infants constituting the majority. Therefore, the deterioration in pelvic peristalsis may be more irreversible when detected in late childhood or adult age. Kaura et al.[13] reported a success rate of 70% in adults and 90.9% in children with GH. As shown in our series in which only pelvic reduction was performed, satisfactory drainage patterns and improvement of APD in GH patients were achieved after pyeloplasty. Pelvic reduction may improve pelvic drainage, but according to our results, we think that nephropexy and nephroplication may not be necessary in pediatric age groups.

Levitt et al.[24] performed 15 ureterocalicostomies (UC) as the primary treatment for UPJO. Ansari et al.[25] reported 25 children who underwent ureterocalicostomy and claimed that UC had excellent outcomes in children with GH due to primary and secondary UPJO. In our series, only one patient with a short ureter underwent UC as a reoperation. Based on our series demonstrating significant improvement in patients' drainage patterns in MAG3 scintigraphy, we think UC will not be the first treatment of choice in pediatric age groups but can be chosen in secondary surgery or patients with short ureters.

Study Limitations

The limitation of this study is that it was a retrospective analysis and involved a small number of patients. However, as far as we know, even though the scarce number of patients were included in this series, it has the longest follow-up period where patients in the pediatric age group with GH were monitored. The long-term preservation of renal function and improvement of PT has been demonstrated, when the patients who had undergone renal scanning at postoperative first year and in the long-term were compared.

CONCLUSION

Postoperative long-term outcomes were satisfactory in pediatric patients with GH due to UPJO and postoperative renal function and PT improved in patients younger than 1 year of age.

Since reduction pyeloplasty provides sufficient urinary clearance, nephropexy, and nephroplication are not necessary for pediatric age.

UC or nephrectomy should not be considered as the first treatment option in infants with GH.

Ethics

Ethics Committee Approval: This study approval by the University of Health Sciences Turkey, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital Clinical Research Ethics Committee (approval number: 2023/09-09-847, date: 22.06.2023).

Informed Consent: All patients were given information about the procedure, and their consent were obtained.

Author Contributions

Surgical and Medical Practices: A.B.U., A.Ş., Concept: A.B.U., Design: A.B.U., A.Ş., Data Collection and Processing: A.B.U., B.S., A.D.P., Analysis and Interpretation: A.B.U., B.S., Literature Search: A.B.U., B.S., A.D.P., Writing: A.B.U., A.Ş.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Crooks KK, Hendren WH, Pfister RC. Giant hydronephrosis in children. J Pediatr Surg. 1979;14(6):844-50. doi: 10.1016/s0022-3468(79)80278-x
2. Sterling WC. Massive hydronephrosis complicated by hydroureter. Report of 3 cases. J Urol. 1939;42:520-33.
3. Baek M, Park K, Choi H. Long-term outcomes of dismembered pyeloplasty for midline-crossing giant hydronephrosis caused by ureteropelvic junction obstruction in children. Urology. 2010;76(6):1463-7. doi: 10.1016/j.urology.2010.05.040

4. Sarhan O, Helmy T, Abou-El Ghar M, Baky MA, El-Assmy A, Dawaba M. Long-term functional and morphological outcome after pyeloplasty for huge renal pelvis. BJU Int. 2011;107(5):829-33. doi: 10.1111/j.1464-410X.2010.09566.x
5. Nerli RB, Reddy MN, Hiremath MB, Shishir D, Patil SM, Guntaka A. Surgical outcomes of laparoscopic dismembered pyeloplasty in children with giant hydronephrosis secondary to ureteropelvic junction obstruction. J Pediatr Urol. 2012;8(4):401-4. doi: 10.1016/j.jpurol.2011.08.008
6. Kim SO, Yu HS, Hwang IS, Hwang EC, Kang TW, Kwon D. Early pyeloplasty for recovery of parenchymal thickness in children with unilateral ureteropelvic junction obstruction. Urol Int. 2014;92(4):473-6. doi: 10.1159/000357144
7. O'Reilly PH. Diuresis renography 8 years later: an update. J Urol. 1986;136(5):993-9. doi: 10.1016/s0022-5347(17)45186-x
8. Sorrentino M. Treatment of giant hydronephrosis. Br J Urol. 1966;38(3):255-61. doi: 10.1111/j.1464-410x.1966.tb09708.x
9. Deming CL. The effects of intrarenal hydronephrosis on the components of the renal cortex. J Urol. 1951;65(5):748-53. doi: 10.1016/S0022-5347(17)68546-X
10. Onen A. An alternative grading system to refine the criteria for severity of hydronephrosis and optimal treatment guidelines in neonates with primary UPJ-type hydronephrosis. J Pediatr Urol. 2007;3(3):200-5. doi: 10.1016/j.jpurol.2006.08.002
11. Dhillon HK. Prenatally diagnosed hydronephrosis: the Great Ormond Street experience. Br J Urol. 1998;81 Suppl 2:39-44. doi: 10.1046/j.1464-410x.1998.0810s2039.x
12. Uson AC, Levitt SB, Lattimer JK. Giant hydronephrosis in children. Pediatrics. 1969;44:209-16.
13. Kaura KS, Kumar M, Sokhal AK, Gupta AK, Purkait B, Saini D, et al. Giant hydronephrosis: still a reality! Turk J Urol. 2017;43(3):337-44. doi: 10.5152/tud.2017.78379
14. Chipde S, Lal H,Gambhir S, Kumar J, Srivastava A, Kapoor R, et al. Factors predicting improvement of renal function after pyeloplasty in pediatric patients: a prospective study. J Urol. 2012;188(1):262-5. doi: 10.1016/j.juro.2012.03.023
15. Li Y, He Y, Zhang W, Song H, Wang T. Factors predicting improvement of differential renal function after pyeloplasty in children of ureteropelvic junction obstruction. J Pediatr Urol. 2022;18(4):504.e1-504.e6. doi: 10.1016/j.jpurol.2022.06.017
16. Bansal R, Ansari MS, Srivastava A, Kapoor R. Long-term results of pyeloplasty in poorly functioning kidneys in the pediatric age group. J Pediatr Urol. 2012;8(1):25-8. doi: 10.1016/j.jpurol.2010.12.012
17. Menon P, Rao KL, Bhattacharya A, Mittal BR. Outcome analysis of pediatric pyeloplasty in units with less than 20% differential renal function. J Pediatr Urol. 2016;12(3):171.e1-7. doi: 10.1016/j.jpurol.2015.12.013
18. Yapanoğlu T, Alper F, Özbey, Aksoy Y, Demirel A. Giant hydronephrosis mimicking an intraabdominal mass. Turk J Med Sci.2007;37:177-9.
19. Hemal AK, Aron M, Wadhwa SN. Nephroplication and nephropexy as an adjunct to primary surgery in the management of giant hydronephrosis. Br J Urol. 1998;81(5):673-7. doi: 10.1046/j.1464-410x.1998.00629.x
20. Kato Y, Yamataka A, Okazaki T, Yanai T, Lane GJ, Kobayashi H, et al. Surgical treatment and outcome of mega-hydronephrosis due to pelviureteric junction stenosis. Pediatr Surg Int. 2006;22(11):911-3. doi: 10.1007/s00383-006-1763-z
21. Jindal L, Gupta AK, Mumtaz F, Sunder R, Hemal AK. Laparoscopic nephroplication and nephropexy as an adjunct to pyeloplasty in UPJO with giant hydronephrosis. Int Urol Nephrol. 2006;38(3-4):443-6. doi: 10.1007/s11255-005-4975-6
22. Shah SA, Ranka P, Dodiya S, Jain R, Kadam G. Giant hydronephrosis: What is the ideal treatment? Indian Journal of Urology. 2004;20(2):118-22.
23. Sataa S, Kerim C, Sami B, Nizar D, Rochdi E, Nidhameddine K, et al. Giant hydronephrosis in adult: What is the best approach? Retrospective analysis of 24 cases. Nephro-Urol Mon. 2011;3(3):177-81.
24. Levitt SB, Nabizadeh I, Javaid M, Barr M, Kogan SJ, Hanna MK, et al. Primary calycoureterostomy for pelvioureteral junction obstruction: indications and results. J Urol. 1981;126(3):382-6. doi: 10.1016/s0022-5347(17)54536-x
25. Ansari MS, Danish N, Yadav P, Kaushik VN, Kakoti S, Kumar A, et al. Role of ureterocalicostomy in management of giant hydronephrosis in children in contemporary practice: Indications, outcomes and challenges. J Pediatr Urol. 2021;17(5):657.e1-657.e7. doi: 10.1016/j.jpurol.2021.06.007

DOI: 10.4274/jbuch.galenos.2024.42492
J Dr Behcet Uz Child Hosp 2024;14(3):153-159

Original Article

The Effectiveness of Computed Tomography Texture Analysis in Distinguishing Wilms Tumor from Neuroblastoma

Bilgisayarlı Tomografi Doku Analizinin Wilms Tümörünü Nöroblastomdan Ayırt Etmedeki Katkısı

Abdi Gürhan[1], İbrahim Altındaş[1], Buket Kara[2], Zuhal İnce Bayramoğlu[3], Mehmet Öztürk[1], Yavuz Köksal[2]

[1]Selçuk University Faculty of Medicine, Department of Radiology, Division of Pediatric Radiology, Konya, Turkey
[2]Selçuk University Faculty of Medicine, Department of Pediatric Hematology and Oncology, Konya, Turkey
[3]İstanbul University, İstanbul Faculty of Medicine, Department of Radiology, Division of Pediatric Radiology, İstanbul, Turkey

ABSTRACT

Objective: This study aimed to determine the effectiveness of computed tomography (CT) texture analysis parameters in distinguishing Wilms tumor (WT) from neuroblastoma (NB).

Method: The research included forty-three patients (23 with WT and 20 with NB) with confirmed diagnoses and CT images. Texture analysis involved seven first-order and nine second-order parameters, with receiver operating characteristic (ROC) analysis performed to differentiate between WT and NB.

Results: Results showed that the median tumor volume was significantly higher in the WT group. Significant differences were found in entropy and homogeneity among first-order parameters. ROC analysis revealed sensitivity and specificity values: 78% and 45% for uniformity, 56% and 85% for entropy and 47% and 75% for sum entropy.

Conclusion: Findings suggest that texture analysis has potential in distinguishing WT from NB in pediatric CT scans, which may reduce the need for repeated scans, additional imaging and invasive procedures, thereby improving patient care and reducing healthcare costs

Keywords: Computed tomography, texture analysis, Wilms tumor, neuroblastoma

ÖZ

Amaç: Bu çalışmanın amacı, bilgisayarlı tomografi (BT) doku analizi parametrelerinin Wilms tümörünü (WT) nöroblastomdan (NB) ayırt etmedeki etkinliğini belirlemektir.

Yöntem: Araştırmaya doğrulanmış tanıları ve BT görüntüleri olan 43 hasta (23 WT ve 20 NB) dahil edildi. Doku analizi, WT ve NB arasında ayrım yapmak için gerçekleştirilen alıcı işletim karakteristiği analizi ile yedi birinci dereceden ve dokuz ikinci dereceden parametre içeriyordu.

Bulgular: Sonuçlar, medyan tümör hacminin WT grubunda anlamlı olarak daha yüksek olduğunu gösterdi. Birinci dereceden parametreler arasında entropi ve homojenlik açısından anlamlı farklılıklar bulunmuştur. ROC analizi, duyarlılık ve özgüllük değerlerini ortaya çıkardı: tekdüzelik için %78 ve %45, entropi için %56 ve %85 ve toplam entropi için %47 ve %75.

Sonuç: Bulgular, doku analizinin pediatrik BT taramalarında WT'yi NB'den ayırt etmede potansiyele sahip olduğunu, bunun da tekrarlanan taramalara, ek görüntülemeye ve invaziv prosedürlere olan ihtiyacı azaltabileceğini, böylece hasta bakımını iyileştirebileceğini ve sağlık hizmeti maliyetlerini azaltabileceğini göstermektedir.

Anahtar kelimeler: Bilgisayarlı tomografi, doku analizi, Wilms tümörü, nöroblastom

Received: 26.07.2024
Accepted: 15.09.2024

Corresponding Author
Mehmet Öztürk,
Selçuk University Faculty of Medicine, Department of Radiology, Division of Pediatric Radiology, Konya, Turkey
drmehmet2121@gmail.com
ORCID: 0000-0001-5585-1476

Cite as: Gürhan A, Altındaş İ, Kara B, İnce Bayramoğlu Z, Öztürk M, Köksal Y. The Effectiveness of Computed Tomography Texture Analysis in Distinguishing Wilms Tumor from Neuroblastoma. J Behcet Uz Child Hosp. 2024;14(3):153-159

INTRODUCTION

Wilms tumor (WT) and neuroblastoma (NB) are the most common intra-abdominal malignant tumors found in adjacent organs in the pediatric age group[(1)]. Because these tumors are frequent in children and typically present with a large abdominal mass, they are often considered in the differential diagnosis of each other, based on clinical and radiological evidence. Diagnostic imaging and laboratory findings are usually helpful in making a definitive diagnosis, but accurately distinguishing between these two tumors can sometimes be challenging[(2)].

Imaging methods are used to gather specific information about tumors, evaluate the type of malignancy, determine the spread of the disease, assess the response to treatment and identify the possible risk of cancer recurrence. However, it is not always possible to distinguish between different types of tumors using

radiological methods. Therefore, a definitive diagnosis of WT or NB before treatment is crucial, as the management and treatment of these tumors are quite different[3]. Nephrectomy is the primary treatment for WT, while neoadjuvant chemotherapy is the main approach for preserving the kidney and its functions in patients with high-risk abdominal NB. WTs typically appear as pseudoencapsulated spherical intrarenal tumors and involve calcification in about 9% of cases, whereas NBs involve calcification in approximately 90% of patients.

Additionally, NB may exhibit radiological findings similar to WT, such as thrombosis in the renal vein, inferior vena cava and right atrium or, in rare cases, lung metastasis. When a large NB infiltrates the kidney, it can be misdiagnosed as an exophytic WT[4].

Computed Tomography Texture Analysis (CTTA) is a new technique that analyses tissue in terms of its structure, microarchitecture, symmetry and homogeneity or heterogeneity[5]. Texture analysis is a quantitative, mathematical image processing method used to assess the spatial heterogeneity of regions of interest in medical imaging and the spatial interrelationships of non-invasive pixel densities. It is used to distinguish between benign and malignant or biologically more aggressive lesions, evaluate tissue microenvironment heterogeneity, tumor grade, tumoral cellular processes, such as hypoxia or angiogenesis, and genetic characteristics such as mutation status, response to treatment and measure fibrosis. In recent years, CTTA has been used in the differential diagnosis of malignant, benign lymphadenopathies in children, in the evaluation of metastatic and non-metastatic lung solid nodules and the diagnosis and grading of immature teratomas[6-8].

This study aimed to retrospectively investigate whether CTTA parameters can distinguish between WT and NB, which are common intra-abdominal tumors in the pediatric age group.

MATERIALS and METHODS

Study Design and Patient Selection

This retrospective study, meticulously conducted at a single-center university hospital and approved by the Selçuk University Local Ethics Committee (approval number: 2021/174, date: 07.07.2021), as well as in observance of the ethical principles outlined in the Declaration of Helsinki, aimed to identify sixty patients with pathological diagnoses of WT and NB. After a thorough process of exclusion and careful selection, a total of forty-three patients (23 WT, 20 NB) with pathological diagnoses and computed tomography (CT) images in the Picture Archiving and Communication System were included in the study.

CT Examination Protocol and Imaging Analysis

The images were obtained using a spiral CT scanner equipped with 64 detectors (Aera, Siemens, Erlangen, Germany) and utilizing low kVp. Axial CT images of the abdomen with a 3.0 mm section thickness were acquired during the venous phase. The specific acquisition parameters were as follows: tube voltage ranging from 110 to 80 kV, tube current from 110 to 180 mA, pitch factor of 0.8, FOV 350-400 mm coverage, single collimation width of 1.2 mm and the use of automatic dose reduction software (CARE Dose 4D). Additionally, a 2 mg/mL non-ionic contrast agent was administered using an auto-injector at a 2-3 mL/sec rate.

CT Texture Analysis

The CTTA was conducted using OLEA research software (Toshiba Medical Systems, Tokyo, Japan) by a researcher with four years of experience in general radiology and another researcher with ten years of experience in pediatric radiology. The process involved placing a free-hand region of interest (ROI) with a radius of approximately one cm in tumor areas without significant necrosis, calcification or vascular structures, in venous phase sequences (Figures 1, 2). Texture analysis included seven first-order statistical parameters (entropy, mean, median, skewness, kurtosis, variance, uniformity) and nine second-order parameters gray matter co-occurrence matrix (GLCOM) (contrast, informal measure of correlation 2, inverse difference moment, maximum probability, sum average, sum entropy, short-run low gray level emphasis and long-run high gray level emphasis), using grey level run length matrix (GLRLM).

Statistical Analysis

All the data was processed in Microsoft Office Excel and then transferred to the SPSS (version 21.0, IBM Corp.) for statistical analysis. The Kolmogorov-Smirnov test assessed the data distribution, which examined skewness and kurtosis. The descriptive statistics of the data included minimum, maximum, mean, standard deviation and median, with interquartile range (IQR). Differences between the mean values of patients' age and tumor volume among the tumor groups, were compared using the Mann-Whitney U test. Additionally, differences between the median values of the first order, GLCOM and

GLRLM parameters among WT and NB were compared using the Mann-Whitney U test. Receiver operating characteristic (ROC) analysis was also conducted to differentiate between WT and NB using the first order, GLCOM and GLRLM parameters. Diagnostic results such as sensitivity, specificity, predictive values and diagnostic accuracy were provided at the 95% confidence interval. A p-value of less than 0.05 was considered statistically significant.

RESULTS

The age range of patients with WT was from 0.1 to 6 years, with a median age of 3 years (IQR: 2-4) and a mean age of 3.17 years with a standard deviation of 1.74. Patients

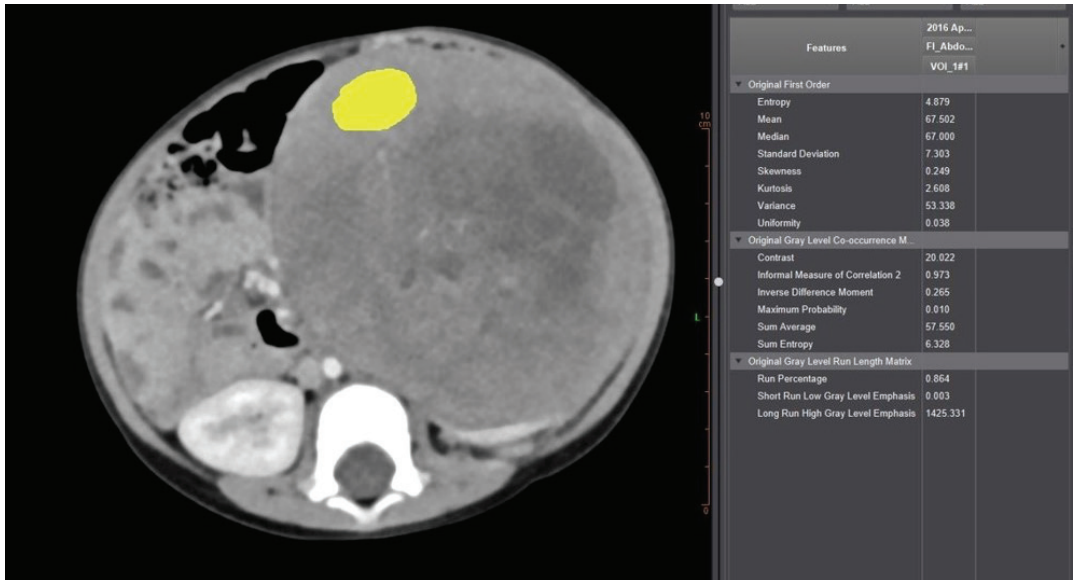

Figure 1. Axial contrast-enhanced CT images: the tissue analysis program monitors the ROI area (yellow area) drawn on the solid mass originating from the left kidney, along with the tissue analysis results of the statistical parameters in the case with WT

CT: Computed tomography, ROI: Region of interest, WT: Wilms tumor

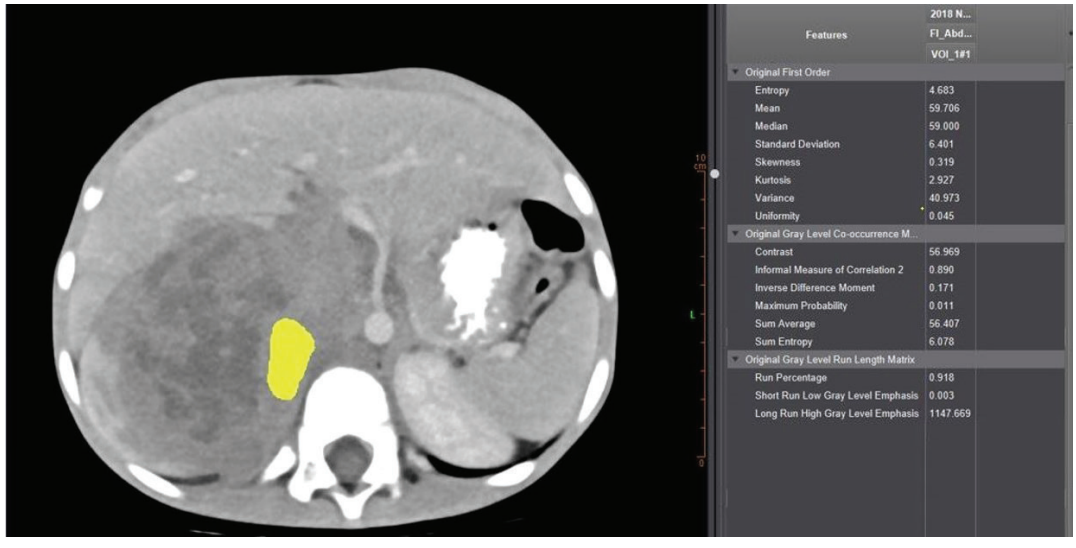

Figure 2. Axial contrast-enhanced CT images: in the case of NB, the tissue analysis program monitors the results of the tissue analysis of the ROI area (yellow area) and statistical parameters drawn on the solid mass in the right adrenal area

CT: Computed tomography, ROI: Region of interest, NB: Neuroblastoma

with NB also had an age range from 0.1 to 6 years, with a median age of 1 year (IQR: 1-3) and a mean age of 2 years with a standard deviation of 1.91. The p-value for age comparison between the two groups was 0.023. In terms of tumor volume, patients with WT had volumes ranging from 32 to 2320 mL, with a median volume of 301 mL (IQR: 106-576) and a mean volume of 429 mL, with a standard deviation of 496. In contrast, patients with NB had tumor volumes ranging from 9 to 1012 mL, with a median volume of 105 mL (IQR: 23-278) and a mean volume of 202 mL with a standard deviation of 255. The p-value for tumor volume comparison was 0.013.

Table 1 displays the median values with IQR of the first-order, GLCOM and GLRM parameters. Among these parameters, entropy and uniformity from the first-order parameters and sum entropy from the GLCOM parameters showed statistically significant differences among the tumor groups. Specifically, entropy (p=0.015) and sum entropy (p=0.038) were significantly higher in the NB group compared to the WT group. At the same time, uniformity (p=0.027) was considerably higher in the WT group compared to the NB group.

Moreover, Table 2 presents the ROC analysis results, including the ROC curve for entropy, uniformity and sum entropy to distinguish WT from NB (Figure 3). Sensitivity, specificity, predictive values, diagnostic accuracies and areas under the curves were calculated for the 95% confidence interval cut-off values.

Table 1. Median and IQR s of the first order, GLCOM and GLRLM parameters compared among WT and NB

	Wilms median (IQR)	Neuroblastoma median (IQR)	p-value
Entropy	4.49 (4.27-4.85)	4.78 (4.58-5.14)	0.015
Mean	58.93 (50.73-71.83)	61.83 (55.26-82.99)	0.16
Median	59 (51-71)	62.5 (55.2-83)	0.18
SD	5.99 (4.75-7.6)	6.49 (5.87-8.67)	0.1
Skewness	0.01 (-0.23-0.5)	0.007 (-0.22-0.25)	0.89
Kurtosis	3.08 (2.76-3.78)	2.92 (2.61-3.21)	0.13
Variance	35.97 (22.57-57.85)	42.15 (34.51-75.59)	0.08
Uniformity	0.05 (0.042-0.059)	0.045 (0.036-0.049)	0.027
Contrast	30.91 (23.7-45.73)	26.72 (21.16-39.65)	0.28
Informal measures of correlation	0.94 (0.92-0.95)	0.95 (0.93-0.97)	0.22
Inverse difference moment	0.22 (0.2-0.25)	0.24 (0.2-0.26)	0.18
Maximum probability	0.015 (0.01-0.016)	0.011 (0.009-0.016)	0.21
Sum average	67.25 (54.6-72.2)	64.4 (62.8-69.75)	0.77
Sum entropy	5.94 (5.63-6.05)	6.06 (5.81-6.25)	0.038
Run percentage	0.87 (0.85-0.89)	0.88 (0.85-0.9)	0.3
Short-run low gray level emphasis	0.003 (0.002-0.005)	0.003 (0.002-0.003)	0.34
Long-run low gray level emphasis	1972 (1327-2121)	1973 (1326-2120)	0.75

p-values are obtained with the Mann-Whitney U test

SD: Standard deviation, IQR: Interquartile range, WT: Wilms tumor, NB: Neuroblastoma, GLCOM: Gray matter co-occurrence matrix, GLRLM: Grey level run length matrix

Table 2. ROC curve analysis results of the significant parameters distinguishing Wilms tum WT roblastoma

	AUC	Cut-off	Sens % (95% CI)	Spes % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	Diagnostic accuracy % (95% CI)
Uniformity	0.7	0.042	78 (56-92)	45 (23-68)	62 (51-71)	64 (41-81)	63 (46-77)
Entropy	0.72	4.55	56 (34-76)	85 (62-96)	81 (58-92)	63 (50-73)	70 (54-82)
Sum entropy	0.68	5.84	47 (26-69)	75 (50-91)	68 (48-84)	55 (43-66)	60 (44-75)

WT: Wilms tumor, AUC: Area under the curve, PPV: Positive predictive value, NPV: Negative predictive value, CI: Confidence interval

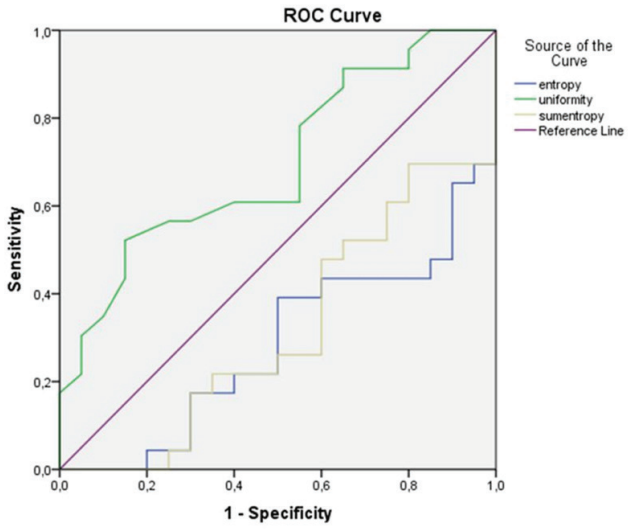

Figure 3. ROC curve of the entropy, uniformity and sum entropy used for distinguishing WT from NB

ROC: Receiver operating characteristic, WT: Wilms tumor, NB: Neuroblastoma

DISCUSSION

NB is the most common solid tumor outside the brain in children, making up 6 to 10% of all pediatric malignancies. It originates from neural crest cells in the adrenal medulla and sympathetic ganglia. Following NB, WT is the second most common pediatric extracranial malignancy, constituting 5 to 6% of pediatric malignancies. The WT is an embryonal renal tumor containing blastemal, stromal and epithelial components. Around 90% of NB s originate in the adrenal gland. Due to their prevalence in the pediatric age group and the typical presentation of a large abdominal mass, these tumors are considered differential diagnoses of each other, from clinical and radiological perspectives.

Differential diagnoses of WT and NB can often be determined through radiological imaging examinations. Features favouring NB include calcification, unclear borders, patient age under two years, crossing the midline, as well as bone and lymph node involvement. Conversely, features of WT include patients aged 3 to 4 years, regular border features, vascular invasion, paw finding and lung metastases. However, radiological differentiation may not always be possible and a definitive diagnosis usually requires a histopathological examination.

While histopathological examination is considered the gold standard for tumor diagnosis, typing and grading in oncological diseases, the medical field is making significant efforts to develop non-invasive methods for prognosis determination, which would reduce the need for treatment and preoperative biopsy[9]. Tissue analysis is a non-invasive, mathematical method that evaluates the spatial heterogeneity of regions of interest in medical imaging[10]. Tissue analysis techniques, first used in radiology by Sutton and Hall[11] in 1972, have become increasingly popular in today's medicine, particularly in the diagnosis, classification and treatment follow-up of oncological diseases. Descriptive statistics revealed that NB was more common in the first two years of age and WT was more common in the 3 to 4 years age group, in line with existing literature. While the size at the time of diagnosis was not previously significant for differentiation in both tumors, this study's results revealed a considerable p-value, indicating that Wilms's tumor was more critical at the time of diagnosis[12].

In this research, we explored the effectiveness of CTTA in distinguishing between WT and NB. Texture analysis assesses the diversity of the cancer and evaluates it based on the disparities in brightness between the examined region and the background signal intensity. Regarding the significant texture parameters in our study, uniformity measures the consistency of gray-level densities within an image or region ROI. Maximum uniformity is achieved when all pixels in an image or ROI, have the same gray level density. Entropy, a measure of heterogeneity, reflects the randomness of the density distribution in the analyzed image. Entropy is at its peak when all densities in the matrix have equal probability. Sum entropy, another indicator of heterogeneity, is calculated by summing the differences between the density values of neighbouring pixels. No prior studies in the literature compare WT and NB regarding texture parameters. In 2009, Shin et al.[13] utilized texture analysis in the differential diagnosis of WT, rhabdoid tumor and clear cell renal sarcomas through ultrasonography, yielding significant results in various texture parameters, such as sum mean, maximum probability and inverse difference moment. Cahalane et al.[6] stated that the use of CTTA features in the study conducted by Pediatric CT, increases the usefulness of pediatric CT in differentiating the difference between benign lymphadenopathy and malignant lymphadenopathy, that it should be added to CT protocols, that it has great potential to aid in the characterization of ambiguous lymph nodes and that it will reduce associated radiation exposure, as well as the need for tissue sampling with follow-up imaging. Our

study is the first to describe the CT texture parameters for both WT and NB.

WT more commonly contains cystic-necrotic areas and bleeding, while calcification is more common in NB. Both tumors appear heterogeneous in radiological and pathological terms. This study aimed to evaluate the microscopic heterogeneity by measuring the tumors' cystic, hemorrhagic and calcific regions. The study found that the uniformity was higher in WT, while the entropy and total entropy were higher in NB, indicating that NB is more heterogeneous at the microscopic level. The study also suggested that specific parameters of the Bi-dimensional Texture Analysis may have good diagnostic performance (area under the curve >0.7) in differentiating NB from WT.

Study Limitations

Our study has some limitations. Firstly, it was conducted with limited WT and NB cases due to its retrospective and single-center nature. Secondly, since the masses are heterogeneous, ROI measurements were made from the solid part, which may affect the tissue analysis parameters. Third, given the reproducibility of the results, this study only analyzed seven first-order and nine second-order parameters, which did not cover all known tissue features. Since this study is a preliminary attempt to use CTTA to identify and rank the 16 parameters of IT, further research will delve deeper into this area with the support of artificial intelligence and additional parameters. Finally, given the relatively limited research on tissue analysis of CT, the contribution of all tissue features to clinical interpretation has yet to be fully recognized. Future research is required to accumulate additional experience in this field, in order to further validate and elucidate the relevance and mechanisms of textural features in clinical practice.

CONCLUSION

The research presented in this study illustrates the potential of utilizing textural analysis to differentiate between WT and NB when examining CT scans of pediatric patients. If successfully implemented in standard clinical practice, this method can minimize the requirement for repetitive follow-up scans, additional imaging and invasive tissue sampling procedures. By incorporating tissue analysis into the existing pediatric abdominal CT protocols, medical professionals may be better equipped to accurately diagnose and differentiate between WT and NB using imaging alone. However, further comprehensive studies with larger sample sizes remain essential to validate the practicality of distinguishing between WT and NB, within real-world clinical environments.

Ethics

Ethics Committee Approval: The study was approved by the Selçuk University Local Ethics Committee (approval number: 2021/174, date: 07.07.2021).

Informed Consent: Retrospective study.

Author Contributions

Concept: A.G., B.K., Z.İ.B., M.Ö., Design: A.G., İ.A., B.K., Z.İ.B., M.Ö., Data Collection and Processing: A.G., İ.A., B.K., M.Ö., Y.K., Analysis and Interpretation: İ.A., Z.İ.B., M.Ö., Y.K., Literature Search: M.Ö., Y.K., Writing: M.Ö.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Kim S, Chung DH. Pediatric solid malignancies: neuroblastomaand Wilms' tumor. Surg Clin North Am. 2006;86(2):469-87. doi:10.1016/j.suc.2005.12.008
2. Brisse HJ, McCarville MB, Granata C, Krug KB, Wootton-Gorges SL, Kanegawa K, et al. Guidelines for imaging and staging ofneuroblastic tumors: consensus report from the InternationalNeuroblastoma Risk Group Project. Radiology. 2011;261(1):243-57.doi: 10.1148/radiol.11101352
3. Grosfeld JL. Neuroblastoma. In: Grosfeld JL, O'Neill JA, FonkalsrudEW, Coran AG (Eds). Pediatric Surgery. Elsevier Science:Philadelphia; 2006:467-94. https://www.academia.edu/31970633
4. Gaetan G, Ouimet A, Lapierre C, Teira P, Sartelet H. Neuroblastomapresenting like a Wilms' tumor with thrombus in inferior venacava and pulmonary metastases: a case series. Springerplus.2014;3:351. doi: 10.1186/2193-1801-3-351
5. Lubner MG, Smith AD, Sandrasegaran K, Sahani DV, Pickhardt PJ.CT texture analysis: definitions, applications, biologic correlatesand challenges. Radiographics. 2017;37(5):1483-503. doi: 10.1148/rg.2017170056
6. Cahalane AM, Kilcoyne A, Tabari A, McDermott S, Gee MS. Computed tomography texture features can discriminatebenign from malignant lymphadenopathy in pediatric patients:a preliminary study. Pediatr Radiol. 2019;49(6):737-45. doi: 10.1007/s00247-019-04350-3
7. Cho YJ, Kim WS, Choi YH, Ha JY, Lee S, Park SJ, et al. Computerized texture analysis of pulmonarynodules in pediatric patients with osteosarcoma: Differentiationof pulmonary metastases from non-metastatic nodules. PLoSOne. 20198;14(2):e0211969. doi: 10.1371/journal.pone.0211969
8. Qi X, Wang X, Zhao X, Teng S, Zhou G, Zeng H. CT texture analysis of pediatric teratomas-associations with identification

and grading of immatureteratoma. Research Square; 2024. doi: 10.21203/rs.3.rs-4534699/v1

9. Meyer JS, Harty MP, Khademian Z. Imaging of neuroblastoma andWilms' tumor. Magn Reson Imaging Clin N Am. 2002;10(2):275-302.doi: 10.1016/s1064-9689(01)00010-1
10. Soni N, Priya S, Bathla G. Texture analysis in cerebral gliomas: Areview of the literature. AJNR Am J Neuroradiol. 2019;40(6):928-34.doi: 10.3174/ajnr.A6075
11. Sutton RN, Hall EL. Texture measures for automatic classificationof pulmonary disease. IEEE Trans Comput. 1972;100:667-76. doi:10.1109/T-C.1972.223572
12. Lowe RE, Cohen MD. Computed tomographic evaluation ofWilm's tumour and neuroblastoma. Radiographics. 1984;4(6):915-28.doi: 10.4236/ojrad.2016.61004
13. Shin HJ, Kwak JY, Lee E, Lee MJ, Yoon H, Han K, et al. Textureanalysis to differentiate malignant renal tumors in childrenusing gray-scale ultrasonography images. Ultrasound Med Biol. 2019;45(8):2205-12. doi: 10.1016/j.ultrasmedbio.2019.03.017

DOI: 10.4274/jbuch.galenos.2024.49260
J Dr Behcet Uz Child Hosp 2024;14(3):160-166

Original Article

Determining the Chronological Age of Children Living in the Mediterranean Region Using Different Radiological Methods and Age Estimation Methods

Akdeniz Bölgesinde Yaşayan Çocukların Kronolojik Yaşlarının Farklı Radyolojik Yöntemler ve Yaş Tahmin Yöntemleri Kullanılarak Belirlenmesi

Berna Kuter[1], Ceren Sağlam[2], Fahinur Ertuğrul[2], Neşe Güler[3]

[1]İzmir Democracy University Faculty of Dentistry, Department of Paediatric Dentistry, İzmir, Turkey
[2]Ege University Faculty of Dentistry, Department of Paediatric Dentistry, İzmir, Turkey
[3]İzmir Democracy University Faculty of Education, Department of Measurement and Evaluation in Education, İzmir, Turkey

ABSTRACT

Objective: The aim of this study was to evaluate the suitability of three age estimation methods, using different radiological techniques, for estimating the chronological age (CA) of children living in the Mediterranean region, and whether these methods can be used in forensic procedures.

Method: A total of 1296 digital orthopantomographic and hand-wrist radiographs of 648 children aged between 7 and 16 years were evaluated. Fishman, Willems and Nolla age estimation methods were used to estimate CA.

Results: Chronological and dental age correlated with the Nolla and Willems methods (NM and WM) in both boys and girls. There was no statistically significant difference between upper canine age estimation and CA using the NM in children aged 7-11 years in boys and in girls. There was no statistically significant difference between the NM upper canine age estimation and CA in children aged 12-14 years in boys.

Conclusion: The WM may be suitable for estimating CA in boys and girls aged 7 and 14 years. The Fishman method may be suitable for estimating CA in girls aged 12-14 years. The NM of upper canine age estimation can also be used to estimate CA.

Keywords: Nolla method, Fishman method, Willems method, age determination, age estimation

ÖZ

Amaç: Bu çalışmanın amacı, Akdeniz bölgesinde yaşayan çocukların kronolojik yaşlarını tahmin etmek için farklı radyolojik teknikler kullanan üç yaş tahmin yönteminin uygunluğunu ve bu yöntemlerin adli prosedürlerde kullanılıp kullanılamayacağını değerlendirmektir.

Yöntem: Yaşları 7 ile 16 arasında değişen 648 çocuğa ait toplam 1296 dijital ortopantomografik ve el-bilek radyografisi değerlendirildi. Kronolojik yaş tahmini için Fishman, Willems ve Nolla yaş tahmini yöntemleri kullanıldı.

Bulgular: Kronolojik ve dental yaş hem erkek hem de kız çocuklarda Nolla ve Willems yöntemleri ile korelasyon gösterdi. Erkeklerde ve kızlarda 7-11 yaş arası çocuklarda Nolla yöntemi ile üst kanin yaş tahmini ve kronolojik yaş arasında istatistiksel olarak anlamlı bir fark yoktu. Erkeklerde 12-14 yaş arası çocuklarda Nolla yöntemi ile üst kanin diş yaşı tahmini ile kronolojik yaş arasında istatistiksel olarak anlamlı bir fark bulunmadı.

Sonuç: Willems yöntemi 7 ve 14 yaşlarındaki kız ve erkek çocuklarda kronolojik yaş tahmini için uygun olabilir. Fishman yöntemi 12-14 yaş arası kız çocuklarında kronolojik yaş tahmini için uygun olabilir. Nolla üst kanin diş yaşı tahmin yöntemi de kronolojik yaşı tahmin etmek için kullanılabilir.

Anahtar kelimeler: Nolla yöntemi, Fishman yöntemi, Willems yöntemi, yaş tayini, yaş tahmini

Received: 09.08.2024
Accepted: 02.10.2024

Corresponding Author
Berna Kuter
İzmir Democracy University Faculty of Dentistry, Department of Paediatric Dentistry, İzmir, Turkey
bernakuter@yahoo.com
ORCID: 0000-0002-1234-8237

Cite as: Kuter B, Sağlam C, Ertuğrul F, Güler N. Determining the Chronological Age of Children Living in the Mediterranean Region Using Different Radiological Methods and Age Estimation Methods. J Behcet Uz Child Hosp. 2024;14(3):160-166

INTRODUCTION

Estimation of chronological, skeletal and dental age is important for both identification and treatment of children[1]. Determining the compatibility of skeletal and dental age with chronological age (CA) by age estimation methods helps to correctly resolve legal and ethical issues, especially in children, during growth and development periods[2].

Dental age estimation methods could provide an accurate assessment of CA[3]. Dental calcification stages are useful measures in age estimation because of a series of recognizable changes. The other method is skeletal age estimation based on the maturation indicators. Skeletal maturation indicators include 11 anatomical regions on the radius, phalanges, and sesamoids. There are many researchers working on this method. Fishman is also one of these researchers. Fishman developed a skeletal maturation assessment method based on hand-wrist radiographs[2], excluding the carpal bones. An important diagnostic tool for age estimation is the hand-wrist radiograph[2], which provides a comprehensive age assessment.

The Willems method (WM) revisited Demirjian's technique based on the developmental stages of teeth[4]. This method contains new charts for each gender, each tooth's score is added, and age is directly converted from the years. The Nolla method (NM) estimates dental age according to the degree of calcification in permanent teeth[5].

Both the maxillary and the mandibular teeth are evaluated according to developmental stage, the scores are added, and the sum is matched with the chart for the value that corresponds to dental age, or tooth age is converted directly to years with age conversion charts. Accurate age estimation with radiography is difficult due to the difficulty of grouping different sample sizes and comparing statistical analysis. Fishman method (FM), NM (canine and first molar) and WM have not previously been evaluated in the same study in children and adolescents.

The applicability of these three age estimation methods was evaluated in children living in the Mediterranean region in this study. In addition, it was evaluated whether canine or first molar maturation stages alone are sufficient to predict CA and whether these methods can be used for forensic procedures in children living in the Mediterranean region.

MATERIALS and METHODS

Subjects

For this study, 1296 digital radiographs of orthopantomographs and hand-wrist radiographs of 648 children were obtained from hospital records. The children whose radiographs were analysed were patients from the provinces of İzmir, Aydın, Manisa, Muğla, Kütahya and Balıkesir who came to the dental clinic with their parents for examination.

Selection Criteria of the Subjects

Inclusion Criteria

Subjects aged between 7 and 16 who visited the Department of radiology at the dental hospital were included in this study. The selection criteria included children with normal growth and development, no serious illness, no trauma to the dental and hand-wrist areas, no congenital or acquired malformations of the hand-wrist and dental regions, and no developmental or hormonal disorders. This study included radiographs taken on the same day and at the same intensity and distance.

Exclusion Criteria

The radiographs that were unclear, not in the proper position, and that had shape anomalies were excluded. When the left side was unsuitable for assessment, the radiographs were excluded. The radiographs without artifacts were evaluated. A total of 1296 digital radiographs of 648 children (383 girls and 265 boys) were evaluated after excluding the radiographs with artifacts.

Study Design and Procedures

This study was conducted retrospectively. Radiographs taken between January 01, 2011 and December 31, 2018 were gathered. It was evaluated by a physician between January 24, 2020 and March 10, 2020. The radiographs were randomly chosen from patients attending the dental hospital. All the radiographs were evaluated by an observer who did not know the children's CA. The ages of children were masked during the process of assessment. After this assessment, each child's CA on the date of the digital radiograph examination was calculated from the date of birth by another researcher. The radiographs were divided into groups according to age and gender. The apex developmental stages of the permanent canines and first molars were taken into account when dividing into the age groups 7-11, 12-14, and 15-16 years.

The skeletal maturation stage of each hand-wrist radiograph was determined according to the FM. A conventional radiograph of the left hand was rated for each subject by an observer, assigned according to the standards, and the average of the ratings was used as the hand-wrist maturation stage.

Dental age estimation was performed according to the WM: seven left mandibular permanent teeth were evaluated and determined according to their developmental stages, and the adapted maturity scores of seven teeth were added to directly obtain the dental age. This was converted into a dental age using published conversion charts for the method.

Radiographs of the upper (UCNM) and lower permanent left canine (LCNM), upper left first molar (UMNM), and lower left first molar (LMNM) were also assessed for dental age according to Nolla's calcification stages.

Ethics

Ethical approval for this study was obtained from the İzmir Democracy University Non-Interventional Clinical Research Ethics Committee (decision number: 2019/04-06, date: 09.12.2019). There was full accordance with ethical principles including those of the World Medical Association's Declaration of Helsinki as revised in 2013. Radiographs taken for treatment were used in this study and weren't taken for research purposes.

Statistical Analysis

Statistical analysis was reported by another researcher who did not evaluate the age determination. Data were analyzed using SPSS 18 (SPSS Inc., Chicago, IL, USA). Statistical significance was set at $p<0.05$. All analyses were performed with a 95% confidence interval. The mean, standard deviation, and standard error for all the groups were calculated, and all analyses were done for boys and girls separately. Since the assumption of the distribution's normality is severely violated for each method according to the Shapiro-Wilk normality test and distribution graphs, for testing the relationship between CA and all methods, Spearman's rank-order correlation coefficients were computed, and for testing the mean differences between CA and all methods, non-parametric tests were used. The differences between the groups were determined by the Mann-Whitney U test in the age variables. The Friedman test was used to evaluate the differences between the mean values of the chronological, skeletal, and dental ages as assessed by skeletal maturation, the first molar, and the canine calcification stages.

RESULTS

The subjects ranged in age from 7 to 16 years with a mean age of 13.06±1.65 years (13.29±1.60 for boys; 12.90±1.67 for girls). The gender and mean age distributions of the children are presented in Table 1.

UMNM and LMNM were not implemented in the children aged between 12 and 16, as they already had mature teeth that could not be used to predict age by assessing the calcification stage. The children aged 12-14 years were categorized into a separate group due to their ongoing canine maturation. The older age group comprised only children aged 15-16 years with delayed teeth.

Correlation Between CA and Age Estimation Methods

Each method showed a different outcome for each gender and age group. There was a correlation between chronological and canine dental ages in both boys and girls aged between 7 and 14 (Table 2).

Seven-eleven years: There were statistically significant correlations of the LCNM, the UCNM, the LMNM, the UMNM, and the WM with CA for boys. In the girls, there were statistically significant correlations between the LCNM, the UCNM, the WM with CA (Table 2).

Twelve-fourteen years: The LCNM, the UCNM, and the WM were statistically significant correlated with CA in both boys and girls (Table 2). FM was statistically significant correlated with CA in girls.

Fifteen-sixteen years: Using all three methods, there were no statistically significant correlations for either boys or girls (Table 2).

Mean Age Differences Between CA and Different Age Estimation Methods

Seven-eleven years: There were no statistically significant mean age differences between CA and the UCNM in both the boys (0.144) and the girls (0.426). There were no statistically significant mean age differences between CA and the WM in the boys (0.782) and the girls (0.352). There were statistically significant mean age differences in both genders between CA and FM, and between CA and the LCNM, the UMNM, the LMNM (Table 3).

Twelve-fourteen years: There was no statistically significant mean age difference between the UCNM and CA in boys (0.192). There were statistically significant

Table 1. Gender and mean age distributions of children

Gender (Age)		A	B	C	D	E	F	G
Boys (7-11)	Mean	10.52	12.03	9.24	9.97	10.00	10.06	10.56
	SD	0.83	0.85	1.96	2.45	1.41	1.24	1.75
Girls (7-11)	Mean	10.59	11.04	9.89	10.38	9.63	9.65	10.43
	SD	0.64	0.87	1.79	2.18	0.72	0.69	1.29
Total (7-11)	Mean	10.57	11.36	9.68	10.25	9.75	9.78	10.48
	SD	0.70	0.98	1.86	2.27	1.02	0.92	1.45
Boys (12-14)	Mean	13.07	12.63	11.67	13.26	-	-	12.56
	SD	0.78	1.28	1.54	1.97	-	-	1.51
Girls (12-14)	Mean	12.85	12.45	11.47	12.26	-	-	12.34
	SD	0.74	1.82	0.97	1.35	-	-	1.42
Total (12-14)	Mean	12.14	12.52	11.55	12.67	-	-	12.43
	SD	0.77	1.63	1.24	1.70	-	-	1.46
Boys (15-16)	Mean	15.32	13.91	12.57	14.38	-	-	13.88
	SD	0.46	2.04	1.02	1.28	-	-	1.23
Girls (15-16)	Mean	15.56	15.10	11.97	12.97	-	-	14.27
	SD	0.46	2.04	1.02	1.28	-	-	1.23
Total (15-16)	Mean	15.44	14.52	12.26	13.66	-	-	14.08
	SD	0.49	2.11	0.78	1.14	-	-	1.14
Boy total (7-16)	Mean	13.29	12.87	11.58	13.11	10.78	10.79	12.63
	SD	1.60	1.59	1.78	2.30	0.70	0.65	1.77
Girl total (7-16)	Mean	12.90	12.65	11.25	12.35	9.91	9.91	12.32
	SD	1.67	2.14	1.30	6.43	0.37	0.37	1.77
Total (7-16)	Mean	13.06	12.74	11.39	12.66	10.27	10.27	12.45
	SD	1.65	1.93	1.52	5.16	0.68	0.67	1.78

A: Chronological age, B: Skeletal age by the Fishman method, C: Lower canine age (Nolla method), D: Upper canine age (Nolla method), E: Lower first molar age (Nolla method), F: Upper first molar age (Nolla method), G: Age determined by Willems method, SD: Standard deviation

Table 2. Correlation between chronological age and age estimation methods

Gender			A	B	C	D	E	F	G
			Sro*/p**	Sro/p	Sro/p	Sro/p	Sro/p	Sro/p	Sro/p
Boys	A	7-11	1	0.149/0.407	0.503/0.003	0.462/0.007**	0.640/0.000**-	0.688/0.000**	0.542/0.001
		12-14		0.143/0.073	0.295/0.000**	0.274/0.000**	-	-	0.319/0.000**
		15-16		0.197/0.122	0.020/0.876	0.68/0.597		-	0.204/0.108
Girls	A	7-11	1	0.120/0.321	0.466/0.000**	0.483/0.000**	0.209/0.080	0.218/0.068	0.442/0.000**
		12-14		0.361/0.000**	0.256/0.000**	0.246/0.000**	-	-	0.316/0.000**
		15-16		0.113/0.365	0.200/0.108	0.200/0.108	-	-	0.138/0.268

*Sro: Spearman's rank-order correlation coefficients, **p: p<0.05 (significant), A: Chronological age, B: Skeletal age by the Fishman method, C: Lower Canine age (Nolla method), D: Upper canine age (Nolla method), E: Lower first molar age (Nolla method), F: Upper first molar age (Nolla method), G: Age determined by Willems method

Table 3. Significant values (p*) for differences between means of CA and age estimation methods

Gender	A-B	A-C	A-D	A-E	A-F	A-G
Boys (7-11)	0.000	0.000	0.144	0.007	0.007	0.782
Girls (7-11)	0.001	0.000	0.426	0.000	0.000	0.352
Boys (12-14)	0.000	0.000	0.192	0.000	0.000	0.000
Girls (12-14)	0.000	0.000	0.000	0.000	0.000	0.000
Boys (15-16)	0.000	0.000	0.000	-	-	0.000
Girls (15-16)	0.745	0.000	0.000	-	-	0.000

*p<0.05 (There is a statistically significant difference between means), A: Chronological age, B: Skeletal age by the Fishman method, C: Lower canine age (Nolla method), D: Upper canine age (Nolla method), E: Lower first molar age (Nolla method), F: Upper first molar age (Nolla method), G: Age determined by Willems method

mean age differences between CA and the other methods (Table 3).

Fifteen-sixteen years: There were statistically significant mean age differences between CA and the other methods (Table 3). There was no statistically significant mean age difference between CA and the FM in girls (0.745).

DISCUSSION

Three different age estimation methods for Mediterranean children with a wide range of ages were evaluated in this study using two different statistical approaches. The results obtained with the three age estimation methods for different age groups varied.

Skeletal age did not show a high correlation with CA in all age groups in either boys or girls in this study. Mohammed et al.[6] reported that there was significant correlation between skeletal age and CA for boys and girls, and, that skeletal age evaluation using the FM could be used as an alternative method for the assessment of mean age. There was only a correlation between CA and skeletal age evaluated by the FM in girls aged 12-14 years in this study. Patil et al.[7] study also reported little correlation between CA and skeletal age evaluated by FM. Ramos et al.[8], who found weak correlation between CA and skeletal. Alkhal, who showed a weak correlation between CA and the FM, and stated that skeletal age was not suitable to estimate CA.[9] Other studies have reported that the FM was suitable to predict CA children in Yemeni[10] and in Bogotanian.[11] Safer et al.[12] also stated that FM could be recommended to estimate CA. Although a significant correlation between CA and skeletal age has been reported, it was stated that there was a significantly lower age estimation with FM in another study[6]. Kiran et al.[1], also reported that there was a significant difference between estimation of skeletal age with FM and estimated CA. The assessment of hand-wrist radiographs for accurate age estimation has been questioned. The research supported by Fishman[2], who devised the method and also reported a significant difference between mean CA and skeletal age. The FM could be said to be the most appropriate method for CA only in girls aged 15-16, in this study.

The NM and the WM correlated with CA in the Mediterranean children in this study. However, there was no correlation between CA and any of the three methods in children aged 15-16 years. There was a correlation between the UCNM and CA and between the LCNM and CA both in the girls and in the boys aged 7-14 years in this study. These results are in line with those of Kiran et al.[1] and Al-Balbeesi et al.[13], showing that the dental development of canines increases with CA. In this study, CA and both UMNM and LMNM were correlated only in boys aged 7-11.

The WM results were correlated to CA and had similar age estimations in both boys and girls aged 7-11, and there were fewer age estimation differences between the WM results and CA for East Mediterranean children compared to other methods in this study. It was reported that their research results were used for dental age estimation in Belgian individuals and were validated in that population but would not be valid in other populations because of dissimilar dental development in various populations[4]. Other studies have reported that the Willems dental maturity scale was the most accurate method for estimating age[14] and had more accurate age estimations than other methods.[15] Esan et al.[16] found that the Demirjian method overestimated CA compared to WM in either gender. For children from North Macedonia, Ambarkova et al.[17] found that Demirjian's method was unsuitable and that the WM showed the most accurate age estimation. In a study in the same region as our study, Ozveren and Serindere[18] reported that the WM had the most accurate outcome

for both genders in all age groups. Moreover, Akkaya et al.[19] reported that the WM could be suggested for CA estimation of Turkish children in forensic practice. Turhal et al.[20] also recommended WM for Turkish children of both genders.

Kiran et al.[1] found no significant difference between CA and dental age when the NM was used to estimate age and stated that the reason why the NM age estimation was closer to the CA for children was probably due to pubertal growth changes. Cortes et al.[21] reported that the NM could be used for estimating CA in children of Spanish origin. However, the NM age estimation was not found to be accurate for children of Southern India[22], and Singh et al.[23], reported similar findings. A study on children in North India found that the permanent mandibular second molar was suitable for age estimation[12]. Khanal et al.[24] found that there was a delayed tooth age in the NM compared to the CA in their research on age estimation for children aged 5-15 in Nepal. However, UCNM predicted a similar age to CA in both boys and girls aged 7-11 in this study and was also the most effective method for similar age estimation to CA in boys aged 12-14.

Güler et al.[25] reported that the skeletal age estimation method gave more accurate results than the dental age method in children of both sexes in their study using different age estimation methods (Cameriere's method).

Study Limitations

Estimation of CA only by calculating canine calcification stages on radiographs could be sufficient for children and adolescents. However, this study's limitation was the lack of sufficient sample size for the children of all Mediterranean countries for dental age estimation.

CONCLUSION

The UCNM and the WM were more accurate estimation methods for CA compared to other methods, which is in agreement with previous research. The WM predicted a similar age to CA in both boys and girls aged 7-11. There were both correlations and similar age estimations to CA with the WM in this age group. The UCNM predicted a similar age estimation to CA in girls aged 7-11 and in boys aged 7-14.

The NM-assessed canine calcification stages on radiographs have the advantage of using a low radiation dose. The estimation of CA by only canine calcification stages on radiographs is easier and cheaper than hand-wrist radiographs. Furthermore, the equipment required are often present in dental clinics.

The NM and the WM could be used for forensic procedures in the Mediterranean region.

• The permanent canine maturation stages by NM could be used to estimation of CA.

• WMs could be used to estimation of CA children in the Mediterranean region.

• The permanent first molar maturation stages by NM could not be a suitable method for estimation of CA.

Ethics

Ethics Committee Approval: Ethical approval for this study was obtained from the İzmir Democracy University Non-interventional Clinical Research Ethics Committee (decision number: 2019/04-06, date: 09.12.2019).

Informed Consent: Retrospective study.

Author Contributions

Concept: B.K., F.E., Design: B.K., F.E., Data Collection and Processing: B.K., C.S., Analysis and Interpretation: B.K., C.S., N.G., Literature Search: B.K., F.E., Writing: B.K.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Kiran S, Sharma V, Srivastava K, Tandon P, Tikku T, Verma S. To establish the validity of dental age assessment using Nolla's method on comparing with skeletal age assessed by hand-wrist radiographs. J Orthod Res. 2013;1(1):438-42. doi:10.4103/2321-3825.112250
2. Fishman LS. Radiographic evaluation of skeletal maturation. A clinically oriented method based on hand-wrist films. Angle Orthod. 1982;52(2):88-112. doi: 10.1043/0003-3219(1982)052<0088:REOSM>2.0.CO;2
3. Kiran S, Sharma V, Tandon P. Correlative and comparative study of Fishman's skeletal maturity indicators with CVMI and chronological age in Lucknow population. Eur J Gen Dent. 2012;1(3):161-5. doi: 10.4103/2278-9626.105356
4. Willems G, Thevissen PW, Belmans A, Liversidge HM. Willems II. Non-gender-specific dental maturity scores. Forensic Sci Int. 2010;201(1-3):84-5. doi:10.1016/j.forsciint.2010.04.033
5. Nolla C. The development of permanent teeth. J Dent Child. 1960;27:254-66. https://www.dentalage.co.uk/wpcontent/uploads/2014/09/nolla_cm_1960_development_perm_teeth.pdf
6. Mohammed RB, Kalyan VS, Tircouveluri S, Vegesna GC, Chirla A, Varma DM. The reliability of Fishman method of skeletal maturation

for age estimation in children of South Indian population. J Nat Sci Biol Med. 2014;5(2):297-302. doi:10.4103/0976-9668.136170

7. Patil N, Maheshwari N, Sharma R, Soni S, Kushwah A. Correlation between chronological age, cervical vertebral maturation and Fishman's skeletal maturity indicators in Central India Population. Orthod J Nepal. 2019;9(2):52-6. doi:10.3126/ojn.v9i2.28415
8. Ramos NAA, Ballesteros Lozano M, Meléndez Ocampo A. Comparative analysis between dental, skeletal and chronological age. Rev Mex Ortod. 2013;1(1):33-7. doi:10.1016/s2395-9215(16)30118-0
9. Alkhal HA, Wong RWK, Rabie ABM. Correlation between chronological age, cervical vertebral maturation and Fishman's skeletal maturity indicators in southern Chinese. Angle Orthod. 2008;78(4):591-6. doi:10.2319/0003-3219(2008)078[0591:CBCACV]2.0.CO;2
10. Alqadi MA, Abuaffan AH. Validity of the Demirjian and Fishman methods for predicting chronological age amongst Yemeni children. Sultan Qaboos Univ Med J [SQUMJ]. 2019;19(1):26-31. doi:10.18295/squmj.2019.19.01.006
11. Pena L, de Mayorga CIG. Skeletal age indicator as chronological age predictor: Comparison between two methods. J World Fed Orthod. 2016;5(3):94-9. doi:10.1016/j.ejwf.2016.09.002
12. Safer AN, Homel P, Chung DD. Lateral comparisons using Fishman's skeletal maturation assessment. Angle Orthod. 2015;85(3):408-12. doi:10.2319/043014-312.1
13. Al-Balbeesi HO, Al-Nahas NW, Baidas LF, Bin Huraib SM, Alhaidari R, Alwadai G. Correlation between skeletal maturation and developmental stages of canines and third molars among Saudi subjects. Saudi Dent J. 2018;30(1):74-84. doi:10.1016/j.sdentj.2017.11.003
14. Maber M, Liversidge HM, Hector MP. Accuracy of age estimation of radiographic methods using developing teeth. Forensic Sci Int. 2006;159(1):568-73. doi:10.1016/j.forsciint.2006.02.019
15. Sehrawat JS, Singh M. Willems method of dental age estimation in children: A systematic review and meta-analysis. J Forensic Leg Med. 2017;52:122-9. doi:10.1016/j.jflm.2017.08.017
16. Esan TA, Yengopal V, Schepartz LA. The Demirjian versus the Willems method for dental age estimation in different populations: A meta-analysis of published studies. PLoS One. 2017;12(11):1-23. doi:10.1371/journal.pone.0186682
17. Ambarkova V, Galić I, Vodanović M, Biočina-Lukenda D, Brkić H. Dental age estimation using Demirjian and Willems methods: Cross sectional study on children from the former Yugoslav Republic of Macedonia. Forensic Sci Int. 2014;234:187.e1-7 doi:10.1016/j.forsciint.2013.10.024
18. Ozveren N, Serindere G. Comparison of the applicability of Demirjian and Willems methods for dental age estimation in children from the Thrace region, Turkey. Forensic Sci Int. 2018;285:38-43. doi:10.1016/j.forsciint.2018.01.017
19. Akkaya N, Yilanci HÖ, Göksülük D. Applicability of Demirjian's four methods and Willems method for age estimation in a sample of Turkish children. Leg Med. 2015;17(5):355-9. doi:10.1016/j.legalmed.2015.04.003
20. Turhal RI, Önem E, Tuğsel Z. Comparison of Willems and Demirjian methods for age estimation in a pediatric Aegean population. J of Ege University School of Dentistry. 2021;42(3):199-204. doi:10.5505/eudfd.2021.36025
21. Cortes MMP, Rojo R, Mourelle Martínez MR, Dieguez Pérez M, Prados-Frutos JC. Evaluation of the accuracy of the Nolla method for the estimation of dental age of children between 4-14 years old in Spain: A radiographic study. Forensic Sci Int. 2019;301:318-25. doi:10.1016/j.forsciint.2019.05.057
22. Patil K. Estimation of dental age by Nolla's method using orthopantomographs among rural free residential school children. Int J Med Res Heal Sci. 2014;3(2):273-7. doi:10.5958/j.2319-5886.3.2.059
23. Singh HV, Kalra N, Tyagi R, Khatri A. Dental age assessment of North Indian origin children using Nolla's method in mandibular second molar. Egypt J Forensic Sci. 2020;10(1):1-7. doi:10.1186/s41935-020-00194-3
24. Khanal S, Acharya J, Shah P. Dental age estimation by Demirjian's and Nolla's method in children of Jorpati, Kathmandu. J Coll Med Sci. 2018;14(3):137-41. doi:10.3126/jcmsn.v14i3.20733
25. Güler ÖÇ, Deniz Y, Arslan S. Comparison of dental and skeletal age estimating methods in children. Acta Stomatol Croat. 2023;57(1):2-11. doi: 10.15644/asc57/1/1

DOI: 10.4274/jbuch.galenos.2024.45548
J Dr Behcet Uz Child Hosp 2024;14(3):167-174

Original Article

Evaluation of Pediatric Deaths Due to Firearm Injuries: A Single-center Experience

Pediatrik Yaş Grubunda Ateşli Silah Yaralamasına Bağlı Ölümlerin Değerlendirilmesi: Tek Merkez Deneyimi

Arif Garbioğlu[1], Emrah Emiral[2], Göksel Vatansever[3]

[1]Zonguldak Bülent Ecevit University Faculty of Medicine, Department of Forensic Medicine, Zonguldak, Turkey
[2]Ankara University Faculty of Medicine, Department of Forensic Medicine, Ankara, Turkey
[3]Ankara University Faculty of Medicine, Department of Child Health and Diseases, Ankara, Turkey

ABSTRACT

Objective: Firearm injuries (FIs) hold a significant place among childhood deaths. Our study aims to raise awareness about preventable FIs by discussing deaths due to FIs in children in the light of relevant national and international studies.

Method: The autopsy files of the cases under the age of 18 due to FIs occured between January 2011 and December 2021 were investigated. Sociodemographic data of the cases, location of the incident, injury site, cause of death, number of shots, shooting distance, type of the firearms used, the owner of the weapon, and the identity of the perpetrator were evaluated.

Results: The study population consisted of 12 (80.0%) male, and 3 (20.0%) female pediatric cases with a mean age of 13.1±5.4 years (median age: 15.0 years). The most common cause of the death was homicide (n=6, 40.0%), and the most frequently used type of firearm was a shotgun. FIs most commonly happened at home (n=8, 53.3%), and most frequently victims died of brain hemorrhage and brain tissue damage (n=11, 31.4%). The firearms used in the incidents mostly belonged to the fathers of the deceased children (n=10, 66.6%).

Conclusion: There is a need to develop multidimensional strategies, including financial support, targeting all segments of society to reduce the number of deaths due to firearms. Additionally, we believe that strict measures to control access to firearms and awareness training to prevent violence will reduce the rates of mortality due to FIs.

Keywords: Autopsy, childhood, firearm, firearm fatalities

ÖZ

Amaç: Ateşli silahlar çocukluk çağı ölümleri arasında önemli bir yere sahiptir. Çalışmamızda, pediatrik grupta ateşli silah ölümlerini uluslararası ve ulusal literatürdeki benzer çalışmalar ışığında tartışarak önlenebilir olan ateşli silah ölümleri konusunda farkındalığı artırmak amaçlanmaktadır.

Yöntem: Ocak 2011 ile Aralık 2021 tarihleri arasında 18 yaş altı ateşli silah yaralanması nedeniyle otopsisi yapılan olguların dosyaları incelenmiştir. Olguların sosyodemografik verileri, olayın meydana geldiği yer, yaralanma bölgesi, ölüm nedeni, atış sayısı, atış mesafesi, ateşli silah türü, silahın ait olduğu kişi, failin kimliği gibi bilgiler değerlendirilmiştir.

Bulgular: Çalışma grubunu oluşturanların %80'i (n=12) erkek, geri kalanı (n=3) kız çocuktu. Olguların yaş ortalaması 13,1±5,4, medyanı 15,0 idi. Olay orijini en sık (n=6, %40,0) cinayet, en sık kullanılan ateşli silah türü av tüfeği idi. En sık olay yeri ev (n=8, %53,3) idi. En sık (n=11, %31,4) ölüm nedeni beyin kanaması ve beyin doku harabiyeti idi. Olayda kullanılan ateşli silah çoğunlukla (n=10, %66,6) ölen çocuğun babasına ait idi.

Sonuç: Ateşli silahlara bağlı ölümleri azaltmak adına toplumun her kesimini hedefleyen finansal desteği içeren çok boyutlu stratejilerin geliştirilmesine ihtiyaç vardır. Ayrıca ateşli silahlara erişim noktasında alınacak sıkı tedbirler ve şiddetin önlenmesine yönelik verilecek bilinçlendirme eğitimlerinin, ateşli silahlara bağlı ölümleri azaltacağına inanmaktayız.

Anahtar kelimeler: Otopsi, pediatrik yaş grubu, ateşli silah, ateşli silah ölümleri

Received: 18.09.2024
Accepted: 30.10.2024

Corresponding Author
Arif Garbioğlu,
Zonguldak Bülent Ecevit University Faculty of Medicine, Department of Forensic Medicine, Zonguldak, Turkey
arif.garbioglu@beun.edu.tr
ORCID: 0000-0002-0440-0963

Cite as: Garbioğlu A, Emiral E, Vatansever G. Evaluation of Pediatric Deaths Due to Firearm Injuries: A Single-center Experience. J Behcet Uz Child Hosp. 2024;14(3):167-174

INTRODUCTION

Deaths due to firearm injuries (FIs) are among increasingly significant public health problems. It is noted that in 2019 alone, more than 250,000 people worldwide lost their lives due to FIs, and homicides accounted approximately 71% of these deaths[1,2]. According to Centers for Disease Control and Prevention, firearm-related homicides increased by 35% in 2020 compared to relevant 2019 data, reaching the highest rate in the past 25 years[3].

In the United States (US), 4.2% of children aged 0-17 years have witnessed a firearm incident[4]. Furthermore, in 2020, firearm-related deaths surpassed traffic accidents to become the leading cause of death among children. The incidence of firearm-related deaths continued to increase in 2021 and did not return to pre-coronavirus disease-19 pandemic levels[5]. Hatchimonji et al.[6] based on 2016 National Trauma Data Bank reports stated that 12% of the 45,288 individuals aged 0-19 years who were injured by firearms between 2010 and 2016 died, with the risk of death being higher at younger ages. According to 2022 census data, 26.5% (22.578.378) of the total population of our country is 0-17 years old. Population projections indicate that the proportion of the child population is in a declining trend over the years. In 2021, the most common causes of death among those aged 5-17 years were external injuries and poisoning[7]. Zeybek et al.[8] have shown that in the pediatric age group suicides are committed mostly by hanging followed by use of firearms.

Infant and child mortality rates are fundamental health indicators that reflect the development level and public health status of countries. Although there has been a global decline in infant and child mortality rates, preventable causes of death still rank high[9]. Determining the epidemiological characteristics of child deaths will guide the implementation of preventive measures. Based on this fact, and in the light of data obtained from relevant national and international studies, our study aims to increase awareness about preventable firearm-related deaths by discussing this issue in the pediatric age group.

MATERIALS and METHODS

Study Design

This study was conducted in compliance with the Declaration of Helsinki-Ethical Principles for Medical Research Involving Human Participants and also the Ankara University Human Research Ethics Committee's approval was obtained (approval number: 107-399-22, date: 01.08.2022). This study is a retrospective analysis of deaths due to FIs among individuals under the age of 18 years in Eskişehir (a province in the northwest part of the Central Anatolia region of Turkey) between January 2011 and December 2021. The flow chart of our research study is presented in Figure 1.

Statistical Analysis

The study data were collected using case forms prepared by the researchers. The case forms inquired sociodemographic data, the location of the incident,

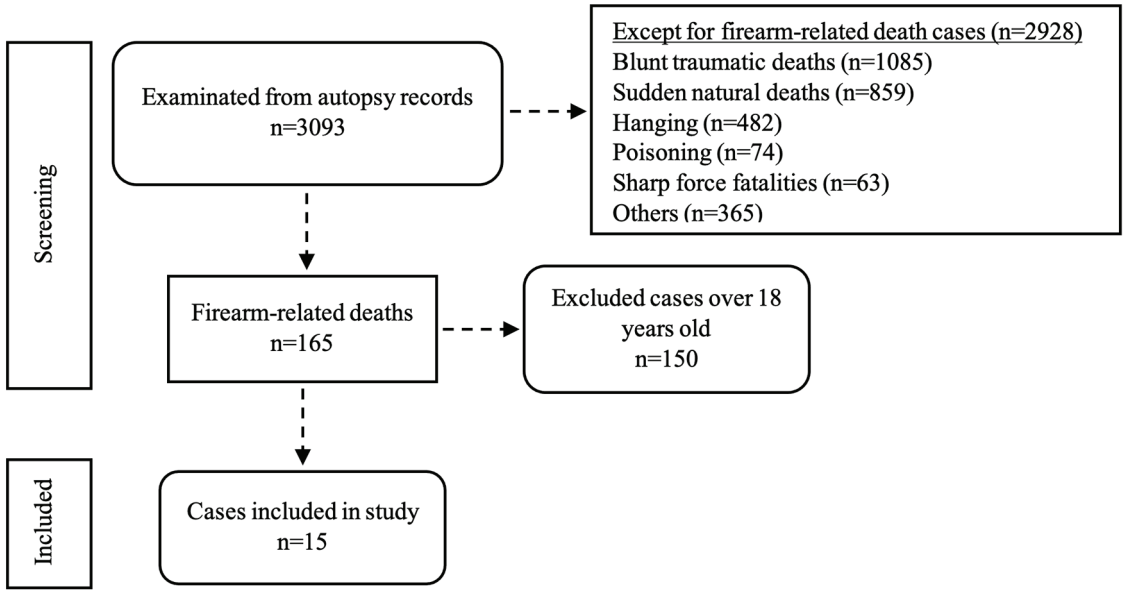

Figure 1. Flow chart

injury site, the cause of death, the number of shots, the shooting distance, the type of firearms used, the owner of the weapon, and the identity of the perpetrator.

Statistical Analysis

The statistical analysis was performed using the IBM SPSS Statistics for Windows [version 20.0 (IBM Inc., Chicago/IL/USA)]. Measured variables are presented as mean ± standard deviation, median, minimum, and maximum values, while categorical data are expressed as numbers (n) and percentages (%).

RESULTS

During the study period, 5.3% (n=165) of the 3,093 forensic deaths were due to FIs. Among those who underwent autopsies due to firearm-related deaths, 9.1% (n=15) were between 0-18 years old. The study population consisted of 12 (80.0%) male and 3 (20.0%) female cases with a mean age of 13.1±5.4 years (age range: 1-18 years; median age: 15.0 years; interquartile range; 13-16 years).

Homicide was the most common cause of the death (n=6, 40.0%), and shotgun was the most frequently used firearm. Victim's home was the most frequently detected crime scene (n=8, 53.3%). The deceased cases who underwent autopsy due to FIs, had (n=10, 66.7%) or had not (n=5, 33.3%) received medical treatment. The most frequent cause of death (n=11, 31.4%) was intracranial bleeding and cerebral parenchymal injury. The firearm used in the incident mostly belonged to the father of the deceased child (n=10, 66.6%). It is noteworthy that the fathers of 2 children who committed suicide were police officers. Demographic and clinical data of the cases are given in Table 1.

The postmortem toxicological examination of the cases could not reveal the suicidal use of sedative, narcotic, or stimulant substances.

DISCUSSION

FIs hold a significant place among childhood deaths both in our country and worldwide. In the US, the incidence rate of firearm-related deaths in children increased by 5.8% from 2018 to 2021[5]. A study conducted in South Africa investigated firearm-related deaths, and found that 1.1% of the deceased cases were

Table 1. Demographic and clinical findings of the cases

Case number	Age (year)/ Sex	Crime scene	Site of injury	Cause of death	Number of GSEW	Origin of death	Range of fire	Types of firearms	Owner of firearm	Killer
1	15/F	Home	Head	ICB and CPI	1	Suicide	Adjacent	Handgun	Father	Own
2	4/M	Home	Chest	IODIB and VDIB	1	Unintentional	Adjacent	Shotgun	Father	Brother
3	9/M	Home	Head	ICB and CPI	1	Unintentional	Close	Shotgun	Father	Brother
4	18/M	Street	Chest, abdomen	IODIB	6	Homicide	Distant	Shotgun	Foe	Foe
5	14/M	Street	Head, chest, abdomen	ICB and CPI and IODIB	3	Homicide	Distant	Shotgun	Foe	Foe
6	15/F	Home	Head	ICB and CPI	1	Suicide	Adjacent	Shotgun	Father	Own
7	16/M	Forest	Neck, chest, extremity	IODIB and VDIB	4	Homicide	Distant	Shotgun	Girlfriend's brother	Girlfriend's brother
8	18/M	Home	Head	ICB and CPI	1	Homicide	Distant	Handgun	Cousin	Cousin
9	16/M	Forest	Head	ICB and CPI	1	Unintentional	Close	Shotgun	Father	Father
10	17/M	Home	Head	ICB and CPI	1	Suicide	Adjacent	Handgun	Father	Own
11	18/M	Forest	Chest, abdomen	IODIB and VDIB	1	Unintentional	Distant	Shotgun	Father	Father
12	1/M	Land	Head	ICB and CPI	1	Homicide	Adjacent	Handgun	Father	Father
13	13/M	Street	Head	ICB and CPI	1	Homicide	Distant	Shotgun	Stranger	Stranger
14	16/F	Home	Head	ICB and CPI	1	Suicide	Adjacent	Handgun	Father	Own
15	7/M	Home	Head	ICB and CPI	1	Unintentional	Close	Handgun	Father	Brother

F: Female, M: Male, GSEW: Gunshot entrance wound, ICB: Intracranial bleeding, CPI: Cerebral parenchymal injury, IODIB: Internal organ damage with internal bleeding, VDIB: Vascular damage with internal bleeding

under the age of 15[10]. Amiri et al.[11], conducted a study in Teheran, and reported the rate of firearm-related deaths as 32.5% among individuals under the age of 20. In a study performed in Diyarbakır province the researchers reported that 34.7% of autopsies conducted between 2014 and 2018 were related to FIs, and 5.8% of these cases autopsies had been performed in children[12]. A study conducted in Muğla province indicated that pediatric cases consisted of 5.9% of firearm-related deaths[13]. Aydın and Yavuz[14] reported a firearm-related mortality rate of 6.07% among individuals under the age of 18. In our study, this mortality rate was 9.1%. As is the case in the rest of the world, firearm-related death rates vary across different regions of our country which are related to the factors such as the approach to violence intervention, access to firearms, socioeconomic inequalities, geographical and cultural differences[5,11].

Based on the data obtained from national and international studies evaluating FIs or deaths in childhood, male children consistuted majority of these cases. In a study by Aydın and Yavuz[14], and a study conducted in Konya[15], and that performed by Çom and Gümüş[12], male children comprised of 69.3%, 68.0%, and 64.2% of the cases injuried or killed by firearms. In the study by Woodruff et al.[16] 76.7% of the cases aged 14 and under who were injuried or killed by firearms between 2005 and 2013 were male victims. In the study by Murhega et al.[17] conducted in the Democratic Republic of Congo, this incidence rate was found to be 63.4%. In as US study, Bayouth et al.[18] revealed that male children consisted of 86.4% of pediatric cases over 20 years of age who were injuried or killed by firearms. Consistent with the literature, the majority of cases (80.0%) in our study were male victims. This phenomenon has been attributed to the curiosity of boys towards dangerous activities[15].

In the US, considering firearm-related homicides in terms of racial and ethnic groups, the highest death rate is among African Americans. From 2012 to 2014, the annual firearm fatality rate among African American children was approximately twice that of American Indian children and four times that of Hispanic children[4]. Ekinci et al.[13] evaluated firearm-related mortality rates in Muğla province, and reported that 1.6% of the cases were of foreign nationality, and half of these cases were part of the resident population. In our study, only 1 (6.6%) resident was a person of foreign nationality while the others (93.3%) were Turkish citizens. The case involving a 16-year-old of Syrian nationality was a homicide victim. According to current data, in Eskişehir, where children constitute 21.0% of the total population, 7.617 foreigners had residence permits[7,19]. Considering that the foreigners with residence permits in Eskişehir constitute 0.84% of the total population, which is below the national average of 1.55%[19,20], the proportion of foreign children in our study is at an expected level.

It has been reported that the firearm-related death rate is higher among children aged 13 and over compared to younger children (0-12 years). This discrepancy in death rates is particularly more pronounced in cases of homicide and suicide[4]. In our study, the rate of homicide in the 13-18 age group was five times higher compared to the 0-12 age group, and suicidal attempts were not observed at all in the 0-12 age group. The lower rate of suicides before adolescence is explained by the rarity of depression and substance abuse in the pre-adolescent age group[21]. In our study, all cases of suicide were aged 15 and above including 1 case with a history of psychiatric illness and substance abuse. While the presence of underlying psychiatric illness in the adolescent age group poses a significant risk for committing suicide, even in the absence of underlying psychiatric illnesses, behavioral components such as age-related impulsivity, environmental factors, and cognitive immaturity or faulty judgment can play an important role in creating a foundation for suicide[21]. In our study, 2 cases committed suicide due to the deterioration of their romantic relationships with their boyfriends, and 1 case who was previously very successful student committed suicide due to a significant decline in academic performance. Family disputes, stress, romantic relationship issues, unrequited love, academic failure, and lack of attention can lead to adolescent crises that may result in suicide. Use of firearms is particularly notable among the methods of suicide in the 15-18 age group[15,22]. Access to firearms is cited as an environmental risk factor in cases of suicide or accidents[15,23]. As is the case in our study, implementation of comprehensive prevention strategies aiming to identify relevant risk factors in health and social services should be considered so as to reduce the risk of suicide among all children, especially those in the late adolescent group.

Wilson et al.[24], indicated that nearly 75% of the perpetrators were the victim's sibling, friend, or acquaintance, and in approximately 30% of the cases, other children witnessed the fatal incident. In our study, 3 cases were unintentionally killed by their siblings, and 2 children were accidentally killed by their fathers. The literature indicates that children who are directly or indirectly exposed to firearm violence experience

a worsening of their mental health problems, with frequently observed symptoms of post-traumatic stress, anxiety, and depression[25]. Therefore, the importance of providing mental health support to children who witness firearm violence is emphasized as a preventive measure in medical practice[24]. However, we believe that it is not solely sufficient to support the emotional well-being of children who are exposed to or witness firearm violence. As indicated in our study, psychological rehabilitation should also be provided to children who unintentionally killed their siblings and to parents who unintentionally killed their children. This is essential for alleviating their suffering and for the recovery of their mental health state.

A study conducted in the US on firearm-related deaths among children aged 5-14 reported a statistically positive association between access to firearm and suicide. It was revealed that in states where firearms are more prevalently available, children are seven times more likely to use firearms and twice as likely to die by suicide[26]. A study evaluating firearm-related deaths in our country between 2013 and 2020, revealed that 93.3% of the firearm-related deaths among child were due to accidents and suicidal attempts[13]. Demirci et al.[15] found that 40% of the these fatalities were due to suicide, and 34% of them were unintentional. In the study by Çom and Gümüş[12], suicide was the leading cause of death (31.3%), followed by homicide (16.4%). In the study by Aydın and Yavuz[14], homicide was the most common cause (32.5%), followed by suicide (29.8%). In our study, the distribution of the firearm-related deaths was relatively close i.e. 6 homicides, 5 unintentional deaths, and 4 suicides. All the unintentionally killed victims were male children. While 3 children were unintentionally killed when their siblings pulled the trigger while playing with a firearm. In the US, from 2003 to 2021, the most common scenario (66.6%) in unintentional pediatric firearm deaths involved children playing with or showing the firearm to someone else when it was discharged[24]. Purchasing realistic toy guns for boys, especially with the advancement of technology, can cause them to perceive all guns, whether real or toy, as playthings. The frequent use of guns in children's games or their enthusiasm for activities involving guns can inevitably lead to unintentional cases of FIs or deaths. Additionally, two children were unintentionally killed by their fathers while hunting wild boars. The practice of parents taking their children along on hunting trips is an important detail that invites unintentional deaths and warrants careful consideration. Both domestic and international studies evaluating firearm-related death cases, reported that male victims constituted the majority of homicide cases[4,14,15]. In our study, the fact that all homicide cases were male is consistent with the relevant literature data.

Keeping firearms at the home is a risk factor for FIs, especially among the pediatric age group[5]. Most unintentional firearm-related deaths in childhood occur at home[24]. Studies investigating firearm-related deaths in the pediatric age group in our country, have revealed that most incidents occur at home[14,15]. In our study, the fact that most incidents involving firearms, including all suicide cases, occurred in the deceased child's home is consistent with the literature data.

According to data from the National Violent Death Reporting System in the US, in 44.6% of unintentional FI deaths among children, the firearms used belonged to the perpetrator's parents[24]. Faulkenberry and Schaechter[27], reported that in 32% of the cases where the firearm owner was identified, the firearm belonged to the father of the victim. Similarly, a study examining child deaths due to FIs in Konya province found that the firearm predominantly belonged to the child's father or his/her relatives (60%)[15]. In our study, consistent with the literature data, the firearm used in the incidents frequently belonged to the father. A study on children presenting to the emergency department due to FIs reported that a family member or a known individual most often shot children[16]. In their study, Faulkenberry and Schaechter[27] found that 84.3% of the cases committed suicide, or killed by a family member, a relative, or a friend. Similarly, in our study, all incidents except for one were committed by the individual themselves, a family member, or someone they knew. As is seen, the inability to prevent access to firearms can result in tragic deaths. This suggestion would also highlight the issue of parental neglect in pediatric cases of firearm-related injuries or deaths.

Relevant national and international literature indicate that in cases when a firearm is fired with suicidal intent, shooting is mostly done from adjacent or nearly close-range, whereas in homicide cases, the firearms are fired from a long distance[11,28,29]. In our study, consistent with the literature data, all suicidal gunshot wounds were caused by adjacent-range shots, whereas the majority of homicide wounds were caused by distant-range shots. The only homicide case involving a adjacent-range shot was a 1-year-old boy who was killed by his father in a fit of rage using a handgun.

In their study on firearm-related deaths, Ekinci et al.[13] found that most cases of firearm-related suicides

and unintentional deaths had a single-entry wound, while most cases of homicide cases had multiple-entry wounds. A study examining firearm-related child deaths in İzmir and its surroundings, indicated that all firearm-related suicide and unintentional cases had a single-entry wound, whereas more than half of the homicide cases had a single-entry wound[14]. The results of our study are consistent with the findings of relevant studies.

Studies on FIs in the US report that the origin of the incident affects the fatality rates at the scene. In firearm-related cases of suicide, medical intervention after the injury is often limited[30]. Mortality rates are higher in cases of gunshot wounds in the head. A study conducted in the US found that 76% of patients with FIs on the head died at the crime scene, and 61% of those who were hospitalized lost their lives[31]. Beaman et al.[32] found that 77.3% of completed suicides had gunshot wounds on the head and these wounds are approximately 2.5 times more fatal than those on the other parts of the body. Another study conducted in the US reported a mortality rate of 39% for FIs in the head and neck[33]. Approximately 75% of all cases in our study, and all suicide-related cases had FIs on the head. Only one of the suicide cases received medical treatment after the FI. The higher fatality rate of head injuries may influence the preference of this region in suicide attempts. It has been reported that hospital admissions for unintentional FIs are at a higher rate compared to suicides[33]. Contrary to the literature, we found that 80% of unintentional cases in our study died at the crime scene without receiving medical intervention. This discrepancy is likely due to our study population consisting solely of fatal cases. Therefore, the exclusion of cases with non-fatal unintentional FIs from the study may explain this discrepancy.

The types of firearms used in pediatric firearm-related deaths vary in national and international studies. In their study on firearm-related deaths among children, Roberts et al.[30] reported that the most commonly used type of firearm in all cases was a handgun, while in the 13-18 age group, the most frequently used firearm was a shotgun. Another study conducted in the US, reported that handguns were the most commonly used type of firearm[16]. In studies examining firearm-related deaths in our country, Demirci et al.[15], and Aydın and Yavuz[14] found that shotguns were used in 66%, and 65.8% of these cases, respectively. While Çom and Gümüş[12] indicated handguns were used in 49.2% of their cases. In our study, the most frequently used type of firearm was a shotgun, while 75% of the suicide cases handguns were used. The most frequent use of shotguns in childhood firearm-related deaths can be explained by the difficulties in concealing shotguns due to their larger size compared to handguns and the common preference for shotguns in rural areas[14,15]. As in our study, the frequent use of handguns in suicide cases may be due to the ease of carrying handguns. Additionally, considering that the fathers of two of our suicide cases were police officers, the failure of law enforcement personnel to adequately secure their firearms at home can lead to fatal consequences.

In our study, use of any sedative, narcotic, or stimulant substances could not be revealed during postmortem toxicological analyses of any cases. However, toxicological examinations should still be performed in cases of mortality due to FIs. This approach helps to determine whether the victim received a sedative or narcotic substance that could have weakened their bodily resistance before the incident or whether they were poisoned by a substance that might have contributed to their death.

Study Limitations

This single-centered study conducted with a limited number of cases makes it difficult to generalize our findings. However, the data obtained from our study can guide new studies conducted with larger sample sizes that include survived cases exposed to FIs. One of the limitations of the study is the lack of data on the socioeconomic status of the cases. Since this a retrospective study, the psychiatric history of the suicide cases prior to the suicide attempts was obtained from the statements of their relatives so detailed psychiatric data of the cases could not be presented.

CONCLUSION

The information obtained from this study may promote the researchers to acquire larger data sets, enabling the identification of relevant epidemiological trends. Establishing a systematic firearm data infrastructure to collect relevant data and identify risk factors could play a crucial role in preventing firearm violence targeting the pediatric population.

Since it is known that low socioeconomic status and high poverty levels increase firearm-related death rates[34], there is a need to develop multidimensional strategies, including financial support targeting all segments of society to reduce firearm-related deaths.

We also believe that strict measures to control access to firearms and awareness training to prevent violence

will reduce firearm-related deaths. The pediatric age group often closely engaged in watching television, the internet, and playing computer games. In this context, since some television shows, movies, social media posts, or computer games may display incidents of firearm violence, we recommend that parents restrict the time passed by their children in front of television, social media, and computers. Furthermore, to prevent easy access to firearms by children, we believe that firearms should be stored securely with safety measures, and should be kept in a gun safe separate from ammunition or in a lockable gun case with a firearm lock.

Ethics

Ethics Committee Approval: This study was conducted in compliance with the Declaration of Helsinki-Ethical Principles for Medical Research Involving Human Participants and also the Ankara University Human Research Ethics Committee's approval was obtained (approval number: 107-399-22, date: 01.08.2022).

Informed Consent: Retrospective study.

Author Contributions

Concept: A.G., E.E., Design: A.G., E.E., Data Collection or Processing: A.G., Analysis or Interpretation: A.G., E.E., G.V., Literature Search: A.G., E.E., G.V., Writing: A.G., E.E., G.V.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Gun deaths by country 2024. World Population Review. Erişim adresi: https://worldpopulationreview.com/country-rankings/gun-deaths-by-country
2. Global Burden of Disease 2016 Injury Collaborators. Global mortality from firearms, 1990-2016. JAMA. 2018;320(8):792-814. doi: 10.1001/jama.2018.10060
3. Centers for Disease Control and Prevention. Firearm deaths grow, disparities widen. Erişim adresi: https://www.cdc.gov/vitalsigns/firearm-deaths/index.html
4. Fowler KA, Dahlberg LL, Haileyesus T, Gutierrez C, Bacon S. Childhood firearm injuries in the United States. Pediatrics. 2017;140(1):1-19. doi: 10.1542/peds.2016-3486
5. Roberts BK, Nofi CP, Cornell E, Kapoor S, Harrison L, Sathya C. Trends and disparities in firearm deaths among children. Pediatrics. 2023;152(3):e2023061296. doi: 10.1542/peds.2023-061296
6. Hatchimonji JS, Swendiman RA, Goldshore MA, Blinman TA, Nance ML, Allukian M 3rd, et al. Pediatric firearm mortality in the United States, 2010 to 2016: a National Trauma Data Bank analysis. J Trauma Acute Care Surg. 2020;88(3):402-7. doi: 10.1097/TA.0000000000002573
7. Türkiye İstatistik Kurumu. İstatistiklerle çocuk, 2022. Erişim adresi: https://data.tuik.gov.tr/Bulten/Index?p=Istatistiklerle-Cocuk -2022-49674
8. Zeybek V, Ata Öztürk HK, Şeydaoğulları Baltacı A, Acar K. Retrospective evaluation of 0-18 age group forensic deaths in Denizli. Turkiye Klin J Foren Sci Leg Med. 2022;19(2):94-101. doi: 10.5336/forensic.2021-87275
9. Statista Research Department. Projected global infant mortality rate 1990 to 2100. Erişim adresi: https://www.statista.com/statistics/673449/projected-global-infant-mortality-rate/
10. Shamase NB, Aldous C, Ntsele SJ. Firearm-related deaths in Gale Street Mortuary, Durban, South Africa from 2004 to 2014. Forensic Sci Int Reports. 2021;3:100183. doi: 10.1016/j.fsir.2021.100183
11. Amiri A, Sanaei-Zadeh H, Towfighi Zavarei H, Rezvani Ardestani F, Savoji N. Firearm fatalities. A preliminary study report from Iran. J Clin Forensic Med. 2003;10(3):159-63. doi: 10.1016/S1353-1131(03)00082-8
12. Çom U, Gümüş B. Evaluation of childhood firearm deaths autopsies in Diyarbakır. Bull Leg Med. 2022;27(1):60-5. doi: 10.17986/blm.1555
13. Ekinci E, Balcı Y, Çallak F, Anolay N. Demographic characteristics and autopsy findings by origin of deaths due to firearm injury-analytical research. Bull Leg Med. 2023;28(1):15-22. doi: 10.17986/blm.1610
14. Aydın F, Yavuz MS. childhood deaths due to firearm injuries in İzmir and nearby cities. Bull Leg Med. 2020;25(1):36-43. doi: 10.17986/blm.2020.v25i1.1362
15. Demirci Ş, Doğan KH, Deniz İ, Büken B, Erkol Z. The deaths related to firearm injuries during the age of childhood in Konya. Bull Leg Med. 2009;14(1):22-9. doi: 10.17986/blm.2009141686
16. Woodruff G, Palmer L, Fontane E, Kalynych C, Hendry P, Thomas AC, Crandall M. Nine years of pediatric gunshot wounds: a descriptive analysis. Prev Med Reports. 2022;28:101890. doi: 10.1016/j.pmedr.2022.101890
17. Murhega RB, Budema PM, Tshimbombu TN, Toha GK, Cikomola FG, Mudekereza PS, et al. Firearm injuries among children due to the Kivu conflict from 2017 to 2020: A hospital-based retrospective descriptive cohort study. Afr J Emerg Med. 2022;12:44-7. doi: 10.1016/j.afjem.2021.11.006
18. Bayouth L, Lukens-Bull K, Gurien L, Tepas JJ, Crandall M. Twenty years of pediatric gunshot wounds in our community: have we made a difference? J Pediatr Surg. 2019;54(1):160-4. doi: 10.1016/j.jpedsurg.2018.10.003
19. Türkiye İstatistik Kurumu. İkamet izinleri. Erişim adresi: https://www.goc.gov.tr/ikamet-izinleri
20. Türkiye İstatistik Kurumu. Toplam nüfus. Erişim adresi: https://cip.tuik.gov.tr/#
21. Dervic K, Brent DA, Oquendo MA. Completed suicide in childhood. Psychiatr Clin North Am. 2008;31(2):271-91. doi: 10.1016/j.psc.2008.01.006
22. Brent DA, Perper JA, Allman CJ, Moritz GM, Wartella ME, Zelenak JP. The presence and accessibility of firearms in the homes of adolescent suicides. A case-control study. JAMA. 1991;266(21):2989-95.

23. Soole R, Kõlves K, De Leo D. Suicide in children: a systematic review. Arch Suicide Res. 2015;19(3):285-304. doi: 10.1080/13811118.2014.996694

24. Wilson RF, Mintz S, Blair JM, Betz CJ, Collier A, Fowler KA. Unintentional firearm injury deaths among children and adolescents aged 0-17 years-National Violent Death Reporting System, United States, 2003-2021. MMWR Morb Mortal Wkly Rep. 2023;72(50):1338-45. doi: 10.15585/mmwr.mm7250a1

25. Holloway K, Cahill G, Tieu T, Njoroge W. Reviewing the literature on the impact of gun violence on early childhood development. Curr Psychiatry Rep. 2023;25:273-81. doi: 10.1007/s11920-023-01428-6

26. Miller M, Azrael D, Hemenway D. Firearm availability and unintentional firearm deaths, suicide, and homicide among 5-14 year olds. J Trauma. 2002;52(2):267-74. doi: 10.1097/00005373-200202000-00011

27. Faulkenberry JG, Schaechter J. Reporting on pediatric unintentional firearm injury-who's responsible. J Trauma Acute Care Surg. 2015;79(3):S2-S8. doi: 10.1097/TA.0000000000000676

28. Karger B, Wissmann F, Gerlach D, Brinkmann B. Firearm fatalities and injuries from hunting accidents in Germany. Int J Leg Med. 1996;108:252-5. doi: 10.1007/BF01369820

29. Karagöz YM, Demirçin Karagöz SD, Atılgan M, Demircan C. An analysis of 133 firearm deaths. Bull Leg Med. 1996;1:122-6. doi: 10.17986/blm.199613149

30. Roberts B, James D, Haft J, Balakrishnan N, Prince J, Sathya C. Wounding patterns in pediatric firearm fatalities. Injury. 2023;54(1):154-9. doi: 10.1016/j.injury.2022.11.072

31. Aarabi B, Tofighi B, Kufera JA, Hadley J, Ahn ES, Cooper C, et al. Predictors of outcome in civilian gunshot wounds to the head. J Neurosurg. 2014;120(5):1138-46. doi: 10.3171/2014.1.JNS131869

32. Beaman V, Annest JL, Mercy JA, Kresnow Mj, Pollock DA. Lethality of firearm-related injuries in the United States population. Ann Emerg Med. 2000;35(3):258-66. doi: 10.1016/S0196-0644(00)70077-1

33. Swendiman RA, Hatchimonji JS, Allukian M 3rd, Blinman TA, Nance ML, Nace GW. Pediatric firearm injuries: anatomy of an epidemic. Surgery. 2020;168(3):381-4. doi: 10.1016/j.surg.2020.02.023

34. Barrett JT, Lee LK, Monuteaux MC, Farrell CA, Hoffmann JA, Fleegler EW. Association of county-level poverty and inequities with firearm-related mortality in US youth. JAMA. Pediatr 2022;176(2):e214822. doi: 10.1001/jamapediatrics.2021.4822

DOI: 10.4274/jbuch.galenos.2024.93798
J Dr Behcet Uz Child Hosp 2024;14(3):175-180

Original Article

Use of Intraosseous Access in the Pediatric Emergency Department: A Single Center Experience

Pediatrik Acil Serviste İntraosseöz Erişim Kullanımı: Tek Merkez Deneyimi

Gülşen Yalçın[1], Özlem Özdemir Balcı[2], Aysel Başer[3], Murat Anıl[1]

[1]İzmir Democracy University, Buca Seyfi Demirsoy Training and Research Hospital, Department of Pediatrics, Division of Pediatric Emergency Medicine, İzmir, Turkey
[2]İzmir Democracy University, Buca Seyfi Demirsoy Training and Research Hospital, Department of Pediatrics, İzmir, Turkey
[3]İzmir Democracy University, Buca Seyfi Demirsoy Training and Research Hospital, Department of Medical Education, İzmir, Turkey

ABSTRACT

Objective: We aimed to compare the efficacy of a battery-powered drill [EZ-intraosseous (IO)] with that of 18-gauge intravenous cannula (18GIVC) needle used for IO access in infants.

Method: This prospective observational study was conducted in the pediatric emergency department between April 1, 2019, and November 3, 2020. Since limited number of EZ-IO needles were available, the first IO accesses were made with 18GIVC needles in all infants. In cases where IO access with 18GIVC failed at the first attempt, the second attempt was made with EZ-IO drill. The cases were divided into two groups: Group 1 (patients with IO access with 18GIVC at first successful attempt) and Group 2 (patients with IO access with EZ-IO drill at the second successful attempt). The Mann-Whitney U test and Fisher's exact or chi-square tests were used for statistical analysis, with level of statistical significance set at $p<0.05$.

Results: Forty six infants were included in the study. In 34 (79.9%) patients the first access with 18GIVC needles was successful. Second attempt with EZ-IO drill was successful in the remaining 12 (26.1%) patients. The cases in Group 1 were younger than in Group 2 ($p<0.001$). All cases aged six months or younger were included in Group 1 ($p<0.001$). The time required for IO access with the EZ-IO drills was statistically significantly shorter compared to the that required for 18GIVC ($p<0.001$). Extravasation was observed in 8 cases (22.2%) within Group 1.

Conclusions: Use of EZ-IO drills provides a quick, efficient, and dependable method for IO access in critically ill infants. If resources are limited, the experienced user can use the 18GIVC hypodermic needle as a last resort for IO access in critically ill infants younger than 6 months.

Keywords: Intraosseous access, EZ-IO, 18-gauge needle, critically ill infant, resource limited situations

ÖZ

Amaç: Süt çocuklarında intraosseöz (IO) erişim için kullanılan pille çalışan matkap (EZ-IO) ile 18-gauge intravenöz kanül (18GIVC) iğnenin etkinliğini karşılaştırmayı amaçladık.

Yöntem: Bu prospektif gözlemsel çalışma, 1 Nisan 2019 ile 3 Kasım 2020 tarihleri arasında çocuk acil servisinde gerçekleştirildi. EZ-IO iğne sayısı sınırlı olduğundan tüm bebeklerde ilk IO girişimi 18GIVC ile yapıldı. İlk denemede 18GIVC'nin başarısız olduğu durumlarda ikinci deneme EZ-IO ile yapıldı. Olgular iki gruba ayrıldı: Grup 1 (ilk başarılı denemede 18GIVC ile IO erişimi olan hastalar) ve Grup 2 (ikinci başarılı denemede EZ-IO ile IO erişimi olan hastalar). İstatistiksel analizlerde Mann-Whitney U testi ile Fisher's exact veya ki-kare testleri kullanılmış olup, $p<0,05$ değeri istatistiksel anlamlılık sınırı olarak kabul edilmiştir.

Bulgular: Çalışmaya 46 çocuk dahil edildi. Bunlardan 34'ünde (%79,9) 18GIVC ile ilk erişim başarılı oldu. Kalan 12 hastada (%26,1) EZ-IO ile ikinci deneme başarılı oldu. Grup 1'deki olgular Grup 2'ye göre daha küçüktü ($p<0,001$). Yaşları ≤6 aylık küçük olguların tamamı Grup 1'deydi ($p<0,001$). EZ-IO ile IO erişim süresi 18GIVC'ye kıyasla istatistiksel olarak daha kısaydı ($p<0,001$). Grup 1'de 8 olguda (%22,2) ekstravazasyon görüldü.

Sonuç: EZ-IO, kritik hasta bebeklerde IO erişimi için hızlı, etkili ve güvenilir bir cihazdır. Kaynaklar sınırlıysa deneyimli kullanıcı, 6 aydan küçük kritik hasta bebeklerde IO erişimi için son çare olarak 18GIVC hipodermik iğneyi kullanabilir.

Anahtar kelimeler: İntraosseous erişim, EZ-IO, 18-gauge iğne, kritik hasta çocuğu, kaynakların sınırlı olduğu durumlar

Received: 26.10.2024
Accepted: 03.11.2024

Corresponding Author
Gülşen Yalçın,
İzmir Democracy University,
Buca Seyfi Demirsoy Training and Research Hospital, Department of Pediatrics, Division of Pediatric Emergency Medicine, İzmir, Turkey
✉ **drgyalcin@gmail.com**
ORCID: 0000-0002-5938-2619

Cite as: Yalçın G, Özdemir Balcı Ö, Başer A, Anıl M. Use of Intraosseous Access in the Pediatric Emergency Department: A Single Center Experience. J Behcet Uz Child Hosp. 2024;14(3):175-180

INTRODUCTION

Achievement of vascular access and administering necessary fluids and drugs in critically ill children convey vital importance. Intraosseous (IO) access is recommended in critically ill patients in whom vascular access is not possible or presumably cannot be performed quickly[1]. In the bone marrow of long bones, the medullar sinuses connect to the veins. Through the IO, all fluids and drugs can be delivered into the bloodstream by inserting the needle through the cortex of a bone into the medullar space. Since these veins are supported by bone matrix, they do not collapse in case of hypoperfusion and shock. Proximal and distal tibia, humerus, and femur are the most preferred regions, and tuberosities around the tibia, proximal to the tibia, are the most frequently used regions for IO access in children[2,3].

There are three types of IO needles: manual IO needles (e.g., Jamshidi needle), spring-loaded devices (e.g., Bone Injection Gun: BIG, WaisMed, Yokneam, Israel), and battery-operated drills (e.g., Arrow® EZ-IO® System, Teleflex, USA). All these devices have certain costs. The most expensive one is the EZ-IO drill. In routine use, hypodermic needles are not recommended as they can be easily clogged[2,4]. Especially in some emergency departments with limited financial resources, the appropriate device for IO intervention may not always be at hand. According to our observations, those who cannot afford to purchase standard IO devices, those who are not trained in the use of devices such as EZ-IO drills, or those who think that hypodermic needles are also an effective option, use the non-recommended over-the-counter devices for IO access. As far as we know, no studies in the literature have compared the effectiveness of hypodermic needles with the EZ-IO device to be used for IO access The aim of this study is to compare the efficacy of the 18-gauge intravenous cannula (18GIVC) and the EZ-IO device for IO access in critically ill infants aged 1-12 months hospitalised in pediatric emergency departments, focusing on IO access time, success rates, and relevant complications, to determine the most efficient and reliable method for clinical use when peripheral venous access cannot be established.

MATERIALS and METHODS

Study Design, Setting and Participants

This prospective observational study was conducted in the pediatric emergency department of a tertiary care teaching and research hospital between 04.01.2019 and 11.30.2020. Children who presented between 08.00 and 17.00 on weekdays were included in the study. All procedures were performed by the same pediatric emergency specialist in order to achieve standardization in the measurements and to minimize the limitations of the study. A total of 3 physicians and 5 nurses were working in each shift in the pediatric emergency department where the study was conducted. Approximately 120,000 patients applied to the pediatric emergency department during the study period.

In cases where peripheral vascular access could not be established within 90 seconds or in 3 consecutive attempts due to hemodynamic instability of the patient, or in cases where the attending physician predicts that the peripheral vascular access cannot be established, IO intervention was performed in the pediatric emergency department. Critically ill infants that required IO access and aged between 1-12 months were included in the study. Patients with extremity trauma, history of IO intervention, and/or chronic bone disease were excluded from the study (Figure 1).

IO Access and Definitions

IO access was achieved using two different methods: manual IO access with a hypodermic needle (an 18GIVC) and IO access with the standard EZ-IO needle (EZ-IO PD15 GA 15 mm) recommended for children weighing between 3 and 39 kg was performed on the left proximal tibia, located 1 cm below and medial to the tibial tuberosity. If the first attempt was IO PD 15 GA 15 mm), recommended for children weighing between 3 and 39 kg. In all cases, the initial attempt was made with the 18GIVC. Due to the limited supply of EZ-IO needles, the EZ-IO was used as a secondary option when attempts with 18GIVC needles were unsuccessful. All IO interventions were performed by the same pediatric emergency specialist. In all patients, IO access was performed on the proximal part of the left tibia located 1 cm inferomedial to the tibial tuberosity. If the first attempt was unsuccessful, the second attempt was made in the corresponding area on the right proximal tibia. Local analgesia was not applied to any patient before the procedure. A nurse recorded the IO access time with a stopwatch in patients in whom IO attempts were successfully achieved. IO access time was not recorded on failed attempts. Once all necessary materials were prepared and the intervention site was sterilized, a chronometer was started as soon as the pediatric emergency specialist pricked the skin with the needle tip. The procedure followed standard

protocols. The doctor indicated the completion of the procedure by saying "OK" upon sensing the entry of the needle tip into the bone marrow, noted by a sudden reduction in resistance after passing through the bone cortex, then the stopwatch was stopped. The duration of this procedure was recorded as the IO access time in seconds. Successful IO access was defined by stable needle fixation and absence of extravasation following bone marrow aspiration and/or fluid administration. Emergency treatment and patient monitoring proceeded according to standard procedures, and the IO access time was noted in minutes. Age, gender, etiology of hemodynamic instability, Glasgow Coma Scale (GCS) score on admission, type of IO access (first successful attempt with 18GIVC or second successful attempt with EZ-IO), IO access time (in seconds), duration of IO access (in minutes), complications, first venous blood gas analysis results obtained in pediatric emergency department, and patient's outcomes (death or discharged alive) were recorded.

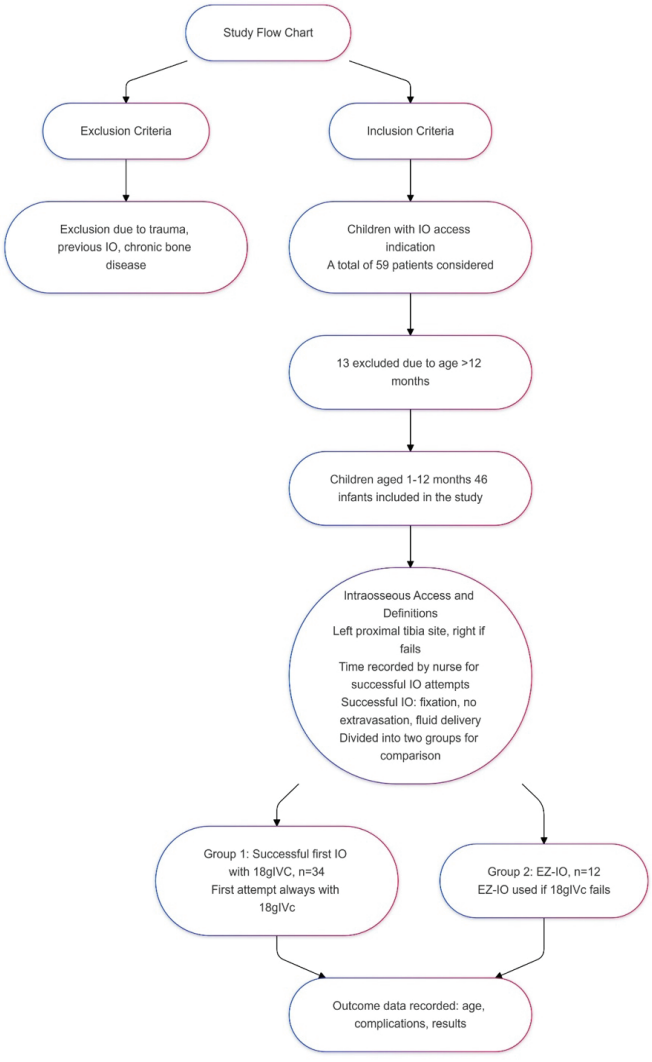

Figure 1. Study flow chart

IO: Intraosseous, 18GIVC: 18-Gauge intravenous cannula, EZ-IO: Battery-powered drill

The cases were divided into two groups and compared: Group 1 (patients with IO access using 18GIVC at first successful attempt) and Group 2 (patients with IO access using EZ-IO device at the second successful attempt).

Statistical Analysis

The data were analyzed with the SPSS 21.00 statistical package program (SPSS Inc©, Chicago, USA). Numerical variables were expressed as medians with interquartile ranges (IQRs), and categorical variables were presented as frequencies and percentages. Comparisons between Group 1 (successful first attempt using 18GIVC) and Group 2 (successful second attempt with EZ-IO) were made. Mann-Whitney U test was applied for numerical data that did not follow a normal distribution. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. Statistical significance was determined at a p-value of less than 0.05.

Ethical Considerations

The study was conducted in accordance with World Medical Association Declaration of Helsinki. Ethical principles for medical research involving human subjects, and approved by the Health Sciences University Turkey, Gazi Yaşargil Training and Research Hospital Clinical Research Ethics Committee (approval number: 633, date: 15.01.2021).

RESULTS

IO access was performed in a total of 59 patients during the study period. Thirteen cases were excluded from the study because they were older than 12 months. Sixteen male and 30 female infants (median age: 6 months; IQR: 3-8; minimum: 1; maximum; 12;) were included in the study. When Group 1 (n=34) and Group 2 (n=12) were compared, patients in Group 1 were younger than in Group 2 (5 months vs. 9 months; p<0.001). All of the cases aged ≤6 months were in Group 1 (p<0.001) There was no significant intergroup difference in terms of the distribution of male and female infants (32.4% male in Group 1 vs. 41.7% in Group 2, p=0.726). The median GCS scores were similar between the two groups [10 (IQR 8-11) in Group 1 vs. 11 (IQR 4-12) in Group 2, p=0.758].

Considering the etiologies of hemodynamic pathologies in patients, hypovolemic shock (n=31; 67.4%), cardiac arrest (n=6 ;13%), respiratory failure (n=6 :13%) and septic shock (n=3; 6.5%) were detected in indicate number (%) of patients. In 34 (79.9%) infants, the first access with 18GIVC was successful. Second attempt with EZ-IO was successful in the remaining 12 (26.1%) patients. No patient required a third attempt (Table 1).

The IO access time with EZ-IO was statistically shorter compared to 18GIVC (7.9 seconds vs. 16.8 seconds) (p<0.001). Extravasation developed in a total of 8 (23.5%) cases. All cases with extravasation were in Group 1. All extravasations developed after the first hour of IO treatment. No other complication was observed except extravasation. Regarding patient outcomes, the mortality rate was slightly higher in Group 2, with 3 patients (25%) compared to 2 patients (5.9%) in Group 1 without any statistically significant intergroup difference (p=0.103). Five (10.8%) cases died (4 in the emergency department and one in the intensive care unit 36 hours after the interventions) (Table 2).

When both groups were compared in terms of the first venous blood gas results obtained in the pediatric emergency department, no statistically significant differences were observed in parameters such as pH, pCO_2, HCO_2, and lactate levels (p>0.05) (Table 3).

At the time of analysis of the study results, while the total costs of 18GIVC needle, and EZ-IO drill used in the study to the hospital were approximately 5, and nearly 26 400 Turkish Liras, respectively.

DISCUSSION

In this study, we found that hypodermic needles, although not routinely recommended, can be used as a last resort for IO access in critically ill infants in a resource-limited pediatric emergency department. IO access was achieved at the first attempt with a hypodermic needle in three-quarters of the cases. As expected, getting IO access with the battery-powered drill is much faster and more efficient. IO access was quickly achieved with EZ-IO drills without wasting time in infants whose IO access could not be achieved in the first attempt with the

Table 1. Comparison of the patients in Group 1 (patients in whom first attempt with 18GIVC was successful) and Group 2 (patients in whom second attempt using instead EZ-IO drill instead of 18GIVC was successful) in terms of age, gender, GCS scores and etiologies of hemodynamic disorder

	Group 1, n=34, n (%)	Group 2, n=12, n (%)	p-value
Age: month median (IQR)	5 (3-6)	9 (8-11)	**<0.001**[1]
≤6 months	28 (82.4)	0	**<0.00**[2]
Male gender	11 (32.4))	5 (41.7)	0.726[2]
GCS, n (IQR)	10 (8-11)	11 (4-12)	0.758[1]
Etiology of hemodynamic disorder			
Hypovolemic shock	24 (70)	7 (58.3)	
Cardiac arrest	4 (11.8)	2 (16.7)	
Respiratory failure	4 (11.8)	2 (16.7)	0.895[3]
Septic shock	2 (5.9)	1 (8.3)	

[1]: Mann-Whitney U test, [2]: Fisher's exact test, [3]: Chi-square test, EZ-IO: Battery-powered drill, 18GIVC: 18-Gauge intravenous cannula, IQR: Interquartile range, GCS: Glasgow Coma Scale

Table 2. Comparison of the patients in Group 1 (patients in whom first attempt with 18GIVC was successful) and Group 2 (patients in whom second attempt using instead EZ-IO drill 18GIVC was successful) in terms of IO access time, duration of IO route, IO access-related complication and patient outcome

	Group 1, n=34	Group 2, n=12	p-value
IO access time, median second (IQR)	16.8 (12.5-19.9)	7.9 (7.1-8.4)	**<0.001**[1]
Duration of IO route, median minute (IQR)	150 (120-180)	125 (96-198)	0.754[1]
Complication, n (%)			
Extravasation	8 (23.5)	0	0.090[2]
Exitus, n (%)	2 (5.9)	3 (25)	0.103[2]

[1]: Mann-Whitney U test, [2]: Fisher's exact test, EZ-IO: Battery-powered drill, 18GIVC: 18-Gauge intravenous cannula, IQR: Interquartile range, GCS: Glasgow Coma Scale, IO: Intraosseous

Table 3. Comparison of the patients in Group 1 (patients in whom first attempt with 18GIVC was successful) and Group 2 (patients in whom second attempt using instead EZ-IO drill 18GIVC was successful) in terms of initial venous blood gas results obtained in the pediatric emergency department

	Group 1, n=34	Group 2, n=12	p-value
pH, median (IQR)	7.12 (6.91-7.20)	7.10 (6.98-7.21)	0.784[1]
pCO_2, median, mmHg (IQR)	56.1 (33.2-79.7)	65.9 (33.4-85.7)	0.762[1]
HCO_3, median, mEq/L (IQR)	11.5 (8.4-17.4)	11.5 (7.3-14.4)	0.599[1]
Lactate, median, mmol/L (IQR)	5.7 (4.2-12)	5.3 (2.3-14.1)	0.634[1]

[1]: Mann-Whitney U test, EZ-IO: Battery-powered drill, 18GIVC: 18-Gauge intravenous cannula, IQR: Interquartile range

hypodermic needle. Extravasations developed in one-fourth of infants who had IO access with a hypodermic needle; however, this complication did not result in termination of IO access in any infant. Studies examining the outcomes of IO accesses using hypodermic needles are very rarely encountered in the current literature and their use for IO access is not routinely recommended. However, we think that this research contributes to the literature in terms of showing that it can be used as a last resort in infants when resources are limited.

The preferred anatomic location for pediatric IO access is the proximal tibia. Various tools can be used to reach the bone marrow from this region. Although inexpensive and easily accessible hypodermic/butterfly needles are user friendly, they are not recommended for routine use as they can be easily clogged with bone fragments. For this reason, they are not used in similar studies especially after the 2000s[5]. In studies conducted before the 2000s; butterfly needles could be used successfully for IO access in infants. The authors stated that since the bone cortex in infants is very thin, the hypodermic needle easily reaches the bone marrow without clogging. In addition, the authors stated that the very few fat cells in the bone marrow of infants increased the chances of being successful when hypodermic needles without a stylet are used for IO access. It was reported that hypodermic needles could be an effective and inexpensive option if financial resources are limited[6]. Based on their experiences, some authors have stated that hypodermic needles can be used when available resources are insufficient; and in case of clogged needles, they suggest practical solutions such as removing the clogged needle and inserting a second needle through the needle tract[7]. IO access options were compared in cadavers of stillborn babies. Post-procedural spectral computed tomography of the cases was taken to confirm the location of the needle. Studies have shown that IO access with a manually inserted hypodermic needle is much more effective than the use of EZ-IO device. The very narrow intramedullary cavity in newborn infants facilitates manual IO access with a hypodermic needle in this age group[8]. Since our study group consisted of infants, IO access with hypodermic needle was successfully achieved in three out of four cases in experienced hands. In our patient group, the age of the cases in which hypodermic needles were successfully inserted was lower than that of the unsuccessful group. In other words, IO access with a hypodermic needle was successful in infants younger than six months of age. This result suggests that hypodermic needles even without stylets may be a successful option for IO access in infants younger than 6 months.

The battery-powered drill has been shown to be effective in IO access in over 90% of children[9,10]. In experienced hands, when the standards are followed, the success rate rises to 100%[2,4,6]. However, in some studies, authors reported that use of manual IO needles had a higher success rate, especially in patients younger than three years old[4,11]. When comparing manual needles and EZ-IO devices, manually inserted IO needles were found to be more successful than EZ-IO devices in infants weighing less than 8 kg. In cases weighing less than 8 kg, IO access was achieved in 5 seconds with manual needle and 13 seconds using EZ-IO drill. In cases weighing more than 8 kg, IO access was achieved in 9 seconds with a manual needle and in 10 seconds with EZ-IO device. As can be seen, manual insertion of an IO needle can be performed faster when compared to EZ-IO in small infants[12]. In general, it is not desirable for the IO access time to exceed 30 seconds[11]. In our study, battery-powered drill was successful in all cases. IO access was achieved in approximately 17 seconds with hypodermic needles and in approximately 8 seconds with an EZ-IO drill. When evaluating these results, it is necessary to consider that the age of the patients who were treated successfully with the hypodermic needle was younger than 6 months, and that those who were treated with EZ-IO drill were infants aged 6-12 months. More importantly, and as a strength of our study, all IO interventions were performed by the same experienced pediatric emergency medicine specialist. Our study results have shown that, in experienced hands, EZ-IO

drills can be successfully and fastly applied for IO access in infants between 6-12 months of age.

IO access is generally a safe practice, and the complication risk is less than 1%. The most common complication is extravasation. It occurs as a result of needle displacement. In terms of compartment syndrome, the extremity where the intervention is made should be evaluated[5,12]. In our study, only extravasation was seen as a complication and all of the extravasations occurred in the hypodermic needle group. Extravasation was observed in approximately one out of every four cases. However, it was not necessary to terminate the procedure of IO access in cases with extravasation. Compartment syndrome did not develop in any of our patients. There were no complications in those with IO access performed using EZ-IO drills. These results have shown once again that IO access is a safe undertaking in experienced hands and when standards are followed.

Study Limitations

The main limitation of the study is the inability to compare the efficacy of other standard IO devices. However, if we had other IO access options in the resource-limited conditions, the hypodermic needle should not be used. Another limitation of the study is the limited number of study participants. The strength of the study is that both hypodermic needles and EZ-IO device were used by the same experienced pediatric emergency medicine specialist. Another feature of the study is that efficacy of IO access was only studied in infants. Thus, the study was carried out with IO devices applied by the same experienced user on infants with similar anatomical features.

CONCLUSION

In experienced hands, EZ-IO drill is a fast, effective, and reliable device for providing IO access in critically ill infants. But, where resources are limited, IO access with an 18-gauge hypodermic needle can be attempted, especially in infants younger than six months. Infants whose IO access was performed using a hypodermic needle, should be carefully monitored for postprocedural complication of extravasation.

Ethics

Ethics Committee Approval: Ethical principles for medical research involving human subjects, and approved by the Health Sciences University Turkey, Gazi Yaşargil Training and Research Hospital Clinical Research Ethics Committee (approval number: 633, date: 15.01.2021).

Informed Consent: Retrospective study.

Author Contributions

Concept: G.Y., Design: G.Y., Data Collection or Processing: G.Y., Ö.Ö.B., A.B., M.A., Analysis or Interpretation: A.B., M.A., Literature Search: Ö.Ö.B., Writing: G.Y.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Topjian AA, Raymond TT, Atkins D, Chan M, Duff JP, Joyner BL, et al. Part 4: Pediatric basic and advanced life support 2020 American Heart Association Guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Pediatrics. 2021;147(Suppl 1):e2020038505D. doi: 10.1542/peds.2020-038505D
2. Buck ML, Wiggins BS, Sesler JM. Intraosseous drug administration in children and adults during cardiopulmonary resuscitation. Ann Pharmacother. 2007;41(10):1679-86. doi: 10.1345/aph.1K168
3. Blumberg SM, Gorn M, Crain EF. Intraosseous infusion: a review of methods and novel devices. Pediatr Emerg Care. 2008;24(1):57-8. doi: 10.1097/pec.0b013e31815f727b
4. Luck RP, Haines C, Mull CC. Intraosseous access. J Emerg Med. 2010;39(4):468-75. doi: 10.1016/j.jemermed.2009.04.054
5. Tobias JD, Ross AK. Intraosseous infusions: a review for the anesthesiologist with a focus on pediatric use. Anesth Analg. 2010;110(2):391-401. doi: 10.1213/ANE.0b013e3181c03c7f
6. Daga SR, Gosavi DV, Verma B. Intraosseous access using butterfly needle. Trop Doct. 1999;29(3):142-4. doi: 10.1177/004947559902900306
7. Krüger C. Intraosseous access in paediatric patients in a developing country setting. Trop Doct. 2001;31(2):118. doi: 10.1177/004947550103100228
8. Fuchs Z, Scaal M, Haverkamp H, Koerber F, Persigehl T, Eifinger F. Anatomical investigations on intraosseous access in stillborns - Comparison of different devices and techniques. Resuscitation. 2018;127:79-82. doi: 10.1016/j.resuscitation.2018.04.003
9. Sørgjerd R, Sunde GA, Heltne JK. Comparison of two different intraosseous access methods in a physician-staffed helicopter emergency medical service - a quality assurance study. Scand J Trauma Resusc Emerg Med. 2019;27(1):15. doi: 10.1186/s13049-019-0594-6
10. Mori T, Takei H, Sasaoka Y, Nomura O, Ihara T. Semi-automatic intraosseous device (EZ-IO) in a paediatric emergency department. J Paediatr Child Health. 2020;56(9):1376-81. doi: 10.1111/jpc.14940
11. Hamed RK, Hartmans S, Gausche-Hill M. Anesthesia through an intraosseous line using an 18-gauge intravenous needle for emergency pediatric surgery. J Clin Anesth. 2013;25(6):447-51. doi: 10.1016/j.jclinane.2013.03.013
12. Pifko EL, Price A, Busch C, Smith C, Jiang Y, Dobson J, et al. Observational review of paediatric intraosseous needle placement in the paediatric emergency department. J Paediatr Child Health. 2018; 54(5):546-50. doi: 10.1111/jpc.13773

DOI: 10.4274/jbuch.galenos.2024.87846
J Dr Behcet Uz Child Hosp 2024;14(3):181-194

Original Article

Association of *Helicobacter pylori*-associated Duodenal Ulcer and Precancerous Findings with Toll-like Receptor-4 Asp299Gly and Toll-like Receptor-9 123T/C Polymorphism and Cag-A, Vac-A in Children

Çocuklarda Helicobacter pylori ile İlişkili Duodenal Ülser ve Prekanseröz Bulguların Toll-like Reseptör-4 Asp299Gly ve Toll-like Reseptör-9 123T/C Polimorfizmi ve Cag-A, Vac-A ile İlişkisi

Ayşegül Cebe Tok[1], Hasan Erhun Kasırga[2], Hörü Gazi[3], Hüseyin Onay[4], Ferda Özkınay[4], Semin Ayhan[5]

[1]Ankara Etlik City Hospital, Clinic of Pediatric Gastroenterology and Hepatology, Ankara, Turkey
[2]Maltepe University Faculty of Medicine, Department of Pediatrics, Division of Pediatric Gastroenterology, İstanbul, Turkey
[3]Manisa Celal Bayar University Faculty of Medicine, Department of Medical Microbiology, Manisa, Turkey
[4]Ege University Faculty of Medicine, Department of Medical Genetics, İzmir, Turkey
[5]Manisa Celal Bayar University Faculty of Medicine, Department of Pathology, Manisa, Turkey

ABSTRACT

Objective: We aim to show whether endoscopic, histopathological and precancerous findings in childhood *Helicobacter pylori (H. pylori)* infection are associated with some changes in the host immune system and some virulence factors of the bacteria. For this purpose, we interpreted the changes in endoscopic and histopathological findings of *TLR-4* and *TLR-9* gene polymorphisms in the innate immune system of the host and cytotoxin associated gene A (Cag-A) and vacuolating cytotoxin A (Vac-A) positivity, the main virulence factors of the bacteria.

Method: Between April 2009 and October 2010, 100 *H. pylori*-positive and 100 *H. pylori*-negative cases were cross-sectionally selected by retrospectively reviewing the files of patients admitted to a tertiary hospital with dyspepsia. After obtaining informed consent, blood samples from these patients were analysed for *TLR-4 [Asp 299 Gly (rs4986790)]* and *TLR-9 [1237 TC (rs5743836)]* gene polymorphisms and for the presence of Cag-A and Vac-A in isolates obtained from pathological specimens.

Results: Poor socio-economic conditions were an important risk factor for *H. pylori.* The presence of Cag-A increased the likelihood of duodenal ulcer. There was no significant difference between *TLR-4 [Asp 299 Gly (rs4986790)]* gene polymorphism and endoscopic and histopathological findings. However, TLR-9 [-1237TC (rs5743836)] polymorphism increased precancerous intestinal metaplasia and atrophy.

Conclusion: The presence of Cag-A increases the risk of duodenal ulceration due to *H. pylori* infection. The TLR-9 [-1237TC (rs5743836)] polymorphism is associated with gastric atrophy and intestinal metaplasia in the pathogenesis of *H. pylori* infection. Studies in large groups of patients are needed.

Keywords: *H. pylori*, toll-like receptors, Vac-A, Cag-A

ÖZ

Amaç: Çocukluk çağı *Helicobacter pylori (H. pylori)* enfeksiyonunda endoskopik, histopatolojik ve prekanseröz bulguların konak immün sistemindeki bazı değişiklikler ve bakterinin bazı virülans faktörleri ile ilişkili olup olmadığını göstermeyi amaçladık. Bu amaçla, konağın doğuştan gelen bağışıklık sistemindeki *TLR-4* ve *TLR-9* gen polimorfizmleri ve bakterinin başlıca virülans faktörleri olan sitotoksin ilişkili gen A (Cag-A) ve vakuolleştirici sitotoksin (Vac-A) pozitifliğinin endoskopik ve histopatolojik bulgulardaki değişiklikleri yorumladık.

Yöntem: Nisan 2009 ve Ekim 2010 tarihleri arasında, dispepsi ile üçüncü basamak bir hastaneye başvuran hastaların dosyaları retrospektif olarak incelenerek 100 *H. pylori*-pozitif ve 100 *H. pylori*-negatif olgu kesitsel olarak seçilmiştir. Bilgilendirilmiş onam alındıktan sonra, bu hastalardan alınan kan örnekleri *TLR-4 [Asp 299 Gly (rs4986790)]* ve *TLR-9 [1237 TC (rs5743836)]* gen polimorfizmleri ve patolojik örneklerden elde edilen izolatlarda Cag-A ve Vac-A varlığı açısından analiz edilmiştir.

Bulgular: Kötü sosyo-ekonomik koşullar *H. pylori* için önemli bir risk faktörüydü. Cag-A varlığı duodenal ülser olasılığını artırmıştır. *TLR-4 [Asp 299 Gly (rs4986790)]* gen polimorfizmi ile endoskopik ve histopatolojik bulgular arasında anlamlı bir fark yoktu. Bununla birlikte, TLR-9 [1237TC (rs5743836)] polimorfizmi prekanseröz intestinal metaplazi ve atrofiyi artırmıştır.

Sonuç: Cag-A varlığı *H. pylori* enfeksiyonuna bağlı duodenal ülserasyon riskini artırmaktadır. TLR-9 [-1237TC (rs5743836)] polimorfizmi, *H. pylori* enfeksiyonunun patogenezinde gastrik atrofi ve intestinal metaplazi ile ilişkilidir. Bu konuda geniş hasta gruplarını içeren çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: *H. pylori*, toll-like reseptörler, Vac-A, Cag-A

Received: 10.10.2024
Accepted: 11.11.2024

Corresponding Author
Ayşegül Cebe Tok,
Ankara Etlik City Hospital, Clinic of Pediatric Gastroenterology and Hepatology, Ankara, Turkey
ayse.cb@gmail.com
ORCID: 0000-0002-7095-8121

Cite as: Cebe Tok A, Kasırga HE, Gazi H, Onay H, Özkınay F, Ayhan S. Association of *Helicobacter pylori*-associated Duodenal Ulcer and Precancerous Findings with Toll-like Receptor-4 A sp299Gly and Toll-like Receptor-9 123T/C Polymorphism and Cag-A, Vac-A in Children. J Behcet Uz Child Hosp. 2024;14(3):181-194

INTRODUCTION

Helicobacter pylori (H. pylori), a gram-negative *microaerophilic* bacterium classified as a class I carcinogen by the World Health Organisation, infects 70-80% of the population in some developing countries and causes peptic ulcer, gastric cancer, or mucosa-associated lymphoid tissue lymphoma[1,2]. *H. pylori* causes severe mucosal inflammation and inhibits acid secretion of parietal cells, leading to gastric atrophy and hypochlorhydria[3]. This clinical outcome has been attributed to the interaction of several factors, including *H. pylori* virulence factors, genetic susceptibility of the host, local innate and adaptive immune responses, and environmental conditions[4]. It has been suggested that *cytotoxin associated gene A (Cag-A)* and *vacuolating cytotoxin A (Vac-A)* genes, which are among the *H. pylori* virulence factors, mainly play a role in epithelial cell damage and chronic inflammation, which may lead to an increase in the risk of gastric cancer[5,6]. Vac-A toxin iniitated the development of vacuoles in the cell membrane, and the presence of the *Cag-A* gene is associated with the development of ulcers, precancerous and cancerous lesions[7-9].

Toll-like receptors (TLRs), which constitute an important part of the innate immune system of the host, recognize structures that are foreign to the body (such as TLR5 flagella, TLR4 lipopolysaccharide, TLR9 unmethylated CpG oligonucleotides) and activate NF-κB and mitogen-activated protein kinases that trigger a common signaling pathway, enabling the immune system to resist the microorganism by increasing the secretion of various cytotoxins such as interleukin (IL)-1, 6, and 8[10-13]. It has been reported that some mutations in TLR4 and TLR9, which are receptors that play an important role in recognizing microorganisms and activating the immune system, are associated with inadequate host response to *H. pylori* infection[14,15]. Two single-nucleotide polymorphisms (SNPs) in the *TLR4* gene, i.e., D299G and T399I, have been linked to hyporesponsiveness and reduced cytokine production in response to endotoxin challenge. The TLR9-1237 TC (rs5743836) variant allele, which has a cytosine to tyrosine substitution in the proximal promoter region, has been associated with the development of *H. pylori*-induced gastric premalignancy[16,17].

To examine the relationship between *H. pylori* infection and the frequency of precancerous lesions in childhood and whether these lesions are caused by the weapons of the microorganism such as Vac-A, Cag-A or by immunity such as TLR receptor [TLR4 Asp299Gly (rs4986790) and TLR9 1237 TC (rs5743836)]. We tried to investigate whether development of these lesions is related to defects in important components of the system.

MATERIALS and METHODS

Between April 2008 and October 2010, using simple random sampling method 200 children were selected for this cross-sectional retrospective study from patients who applied to Celal Bayar University Medical Faculty Pediatric Gastroenterology Clinic and Underwent Gastric Endoscopies. Patient records were examined retrospectively and according to histopathological examination results, 100 *H. pylori*-positive children were classified as Group 1; hundred *H. pylori*-negative children were included in Group 2 (gastritis group). When the patients came for their routine polyclinic check-ups after their treatment was achieved based on their established diagnoses, written information, and consent forms were given to their parents to be read, and signed by them voluntarily if they approved the conduction of the study. Inclusion criteria in our study were as follows: presence of gastrointestinal (GI) symptoms (nausea, heartburn, abdominal pain, vomiting, etc.) consistent with acute gastritis, age between 5 and 18 years, absence of symptoms consistent with infectious disease, and chronic diseases. Exclusion criteria were as follows: age under 5 years, use of antibiotics, proton pump inhibitors or H_2-receptor blockers within the previous 4 weeks, clinical signs and symptoms consistent with infectious disease (fever, diarrhoea), incomplete clinical or laboratory data, parental/guardian refusal to undergo upper GI endoscopy and/or to sign the informed consent form for the participation of their children in the study.

DNA Isolation

DNA was isolated from 2 cc ethylenediaminetetraacetic acid treated blood samples collected from patients and controls. Vitek DNA Identification Kit (Germany) was used for isolation of DNA.

TLR4Asp299Gly (rs4986790) Polymorphism Genotyping

The desired region in the obtained DNAs was amplified by polymerase chain reaction (PCR). Allele-specific PCR method was used for genotyping. This method uses a common reverse primer to distinguish between mutant and normal sequences and allele-specific oligonucleotides designed to amplify normal and mutant sequences. PCR was performed using forward-

C+reverse and forward-G+reverse primer pairs for each sample. PCR products were evaluated by loading them onto a 2% agarose gel. Primer sequences obtained from Thermo Electron Corporation (Rosemount, Minnesota, USA) were used.

TLR9-1237 TC (rs5743836) Polymorphism Genotyping

The desired region was amplified by PCR in the DNA samples. The following primers used in the PCR products were evaluated by loading on a 2% agarose gel. Then, restriction fragment length polymorphism process was applied to PCR products.

Isolation of *H. pylori* from Histopathology Preparations

DNA isolation was performed in 94 of the gastric biopsy samples obtained using High Pure PCR Template Preparation Kit (Roche Diagnostics Co., Germany). The presence of *H. pylori* and the bacterial virulence markers Vac-A and Cag-A in the extracts were assessed by real-time PCR (Roche Light Cycler® 480 II, Germany). The 16S rRNA of *H. pylori* was isolated. The specific regions of the *Vac-A* and *Cag-A* genes were examined.

All endoscopies of the upper digestive tract were performed by the same trained and experienced gastroenterologist. For the histopathological examination, the Giemsa stain was used to detect *H. pylori*, and all of these examinations were also carried out by the same histopathologist.

Ethical Considerations

All the parents/caregivers signed the informed consent for the participation of their children in the study, which was performed in compliance with the World Medical Association Declaration of Helsinki. Ethical principles for medical research involving human subjects. The study was approved by the Ethics Committee of the Manisa Celal Bayar University (approval number: 27, date: 17.03.2012).

Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) v.26.0. Categorical data of pediatric patients were given as numbers and percentages. Data related to the age variable were given as mean, standard deviation, median, minimum and maximum. The suitability of the age variable of the patients to the normal distribution was decided by assessing the skewness and kurtosis values, and it was seen that the data fit to the normal distribution. The reference value taken in normal distribution varied between ±1.5. Chi-square test was used to compare the descriptive characteristics, endoscopic, and histopathologic findings, presence of *TLR4* gene and *TLR9* gene polymorphisms, Cag-A and Vac-A (presence of S and M1/M2), findings of *H. pylori*-positive and-negative patients. Independent samples t-test was used to compare the mean age of *H. pylori*-positive and-negative patients. Pearson's correlation test was used to examine the relationships between *H. pylori*-positivity, Cag-A and Vac-A (presence of s and M1/M2), endoscopic and histopathologic findings in pediatric patients. The correlation coefficient was evaluated as a a presence of a low-level correlation between 0.00-0.30, a medium correlation between 0.30-0.70 and a high correlation between 0.70-1.00. In the whole study, the levels of statistical significance were set at p=0.05 and 0.01.

RESULTS

The characteristics of patients in both study groups are summarised in Table 1. There was no difference between Groups 1, and 2 patients in terms of age, gender and symptomatology. Only socioeconomic status of Group 1 patients were comparativly lower (p=0.044) (Table 1).

When we compared the endoscopic and histopathological findings of the patients in Groups 1 and 2, the severity and frequency of gastritis, duodenitis, duodenal ulcer and antral nodularity were statistically significantly higher in Group 1. While there was no significant difference between Groups 1 and 2 in terms of the presence of TLR4 Asp299Gly and TLR-9 1237 TC polymorphisms, especially the Homozygous for allele C (CC), was more frequently identified in Group 1 patients (Table 2).

When we compare the positivity rates for Cag-A, Vac-A-S1/S2 region and Vac-A M1/M2 region in *H. pylori* isolates obtained from patients in Group 1 and the endoscopic and histopathological findings of the patients; no difference was observed in terms of the distribution of gastric ulcer, duodenal ulcer, presence of reflux, antral nodularity, atrophy, lymphoid aggregation, and intestinal metaplasia (p>0.05) (Table 3).

However, a low level positive correlation was detected between the presence of Cag-A protein and duodenal ulcer (p<0.05). These results showed that as the expression rate of Cag-A protein in patients

Table 1. Comparison of descriptive characteristics of pediatric patients in terms of the presence of *H. pylori*						
Descriptive characteristics of patients		***H. pylori*-positive (n=100)**		***H. pylori*-negative (n=100)**		**p-value**
		n	**%**	**n**	**%**	
Gender	Female	64	64.0	68	68.0	0.654
	Male	36	36.0	32	32.0	
Age (years)	5-12	40	40.0	40	40.0	1.000
	13-18	60	60.0	60	60.0	
Socio-economic status	Appropriate	2	2.0	6	6.0	0.044*
	Middle	68	68.0	77	77.0	
	Low	30	30.0	17	17.0	
Residence	Urban	61	61.0	52	52.0	0.389
	Rural	39	39.0	48	48	
Drinking water	Clean water	28	28.0	30	30.0	0.102
	Tap water	72	72.0	70	70.0	
Abdominal pain	Yes	80	80.0	86	86.0	0.347
	No	20	20.0	14	14.0	
Heartburn	Yes	55	55.0	64	64.0	0.249
	No	45	45.0	36	36.0	
Nausea	Yes	61	61.0	54	54.0	0.391
	No	39	39.0	46	46.0	
Vomiting	Yes	32	32.0	30	30.0	0.878
	No	68	68.0	70	70.0	
		Mean ± SD, med. (min.-max.)		Mean ± SD, med. (min.-max.)		
Aget		12.88±2.88 13 (5-17)		12.72±3.24 13 (5-18)		0.712

*p<0.5, **p<0.01, χ^2: Chi-square test (categorical data), ^{t}: Independent samples t-test, *H. pylori: Helicobacter pylori,* min.: Minimum, max: Maximum, med.: Median, SD: Standard deviation

increases, the frequency of duodenal ulcer will also increase (Table 4).

Since in the *H. pylori*-positive group, only 6 patients were heterozygous carriers of the TLR4 Asp299Gly (rs4986790) polymorphism, statistical evaluation could not be made. However, in the AG genotype in the *H. pylori*-positive group (n=6), duodenitis (n=2; 33.3%), duodenal ulcer (n=1; 16.6%), antral nodularity (n=1; 16.6%), moderate glandular atrophy (n=2; 33.3%) and intestinal metaplasia (n=1; 16.6%) were observed in respective number of patients.

Endoscopic parameters did not differ in the presence of *TLR9* gene 123T/C (rs5743836) polymorphisms in Group 1 (p>0.05). However, in Group 1, the distribution of glandular atrophy, and intestinal metaplasia differed according to the presence or absence of *TLR9* gene polymorphisms (p<0.05). The patients with CC polymorphism had higher rates of glandular atrophy and intestinal metaplasia than patients with homozygous for allele T (TT) and TC polymorphisms (Table 5).

The effect of *TLR9* gene polymorphisms on the presence of intestinal metaplasia was found to be significant chi-square: 26.98, p=0.000, p<0.01. While the presence of the TC allele did not make a significant difference. It was determined that rates of intestinal metaplasia increased significantly in the presence of the CC allele (p<0.05).

The probability of intestinal metaplasia in the presence of *CC* gene polymorphism increased by 46.2-fold when compared with *TT* gene polymorphisms (Table 6).

Similarly, the effect of *TLR9* gene polymorphisms on the presence of glandular atrophy was found to be significant Ki-square=25.29, p=0.000, p<0.01. While the presence of the TC allele did not make a significant difference, the presence of the CC allele significantly increased the rates of glandular atrophy (p<0.05). Considering the odds ratios; the probability of atrophy in the presence of *CC* gene polymorphism was 17.8 times higher than in the presence of *TT* gene polymorphism (Table 6).

Table 2. Comparison of endoscopic and histopathological findings in terms of the presence of *H. pylori* in pediatric patients						
Endoscopic and histopathological findings		***H. pylori*-positivity (n=100)**		***H. pylori*-negativity (n=100)**		
		n	**%**	**n**	**%**	**p-value**
Severity of gastritis	Normal-mild	33	33.0	59	59.0	**<0.001****
	Moderate-severe	67	67.0	41	41.0	
Localization	Antrum-corpus	64	64.0	79	79.0	**0.028***
	Antrum	36	36.0	21	21.0	
Gastritis type	Normal	0	0.0	3	3.0	0.432
	Erythematous-erosive	98	98.0	96	96.0	
	Atrophic	2	2.0	1	1.0	
Duodenitis	No	51	51.0	73	73.0	**0.002****
	Yes	49	49.0	27	27.0	
Gastric ulcer	No	93	93.0	93	93.0	1.000
	Yes	7	7.0	7	7.0	
Duodenal ulcer	No	84	84.0	95	95.0	**0.021***
	Yes	16	16.0	5	5.0	
Esophagitis	No	89	89.0	91	91.0	**0.814**
	Yes	11	11.0	9	9.0	
Antral nodularity	No	13	13.0	40	40.0	**<0.001****
	Mild	16	16.0	31	31.0	
	Moderate	40	40.0	19	19.0	
	Severe	31	31.0	10	10.0	
Chronic inflammation	No	0	0.0	58	58.0	**<0.001****
	Mild	24	24.0	39	39.0	
	Moderate	66	66.0	3	3.0	
	Severe	10	10.0	0	0.0	
Activity	No	19	19.0	97	97.0	**<0.001****
	Mild	29	29.0	3	3.0	
	Moderate	52	52.0	0	0.0	
Glandular atrophy	No	83	83.0	99	99.0	**<0.001****
	Mild	6	6.0	1	1.0	
	Moderate	11	11.0	0	0.0	
Lymphoid aggregation	No-mild	46	46.0	98	98.0	**<0.001****
	Moderate-severe	54	54.0	2	2.0	
Intestinal metaplasia	No	86	86.0	100	100.0	**<0.001****
	Yes	14	14.0	0	0.0	
H. pylori density	No	0	0.0	99	99.0	**<0.001****
	Mild	19	19.0	0	0.0	
	Moderate	70	70.0	1	1.0	
	Severe	11	11.0	0	0.0	
TLR4 Asp299Gly (rs4986790) Polymorphism	AA	94	94.0	94	94.0	**1.000**
	AG	6	6.0	6	6.0	
TLR9 123T/C (rs5743836) Polymorphism	TT	43	43.0	34	34.0	**0.005****
	TC	36	36.0	57	57.0	
	CC	21	21.0	9	9.0	

*p<0.05, **p<0.01, χ^2: Chi-square test, *H. pylori: Helicobacter pylori,* TLR: Toll-like receptor, AA: Homozygous for allele A, AG: Heterozygous, TT: Homozygous for allele T, CC: Homozygous for allele C

Table 3. Distribution of endoscopic and histopathological data according to the presence of Cag-A, Vac-A S1/S2 region, Vac-A M1/M2 region in the *H. pylori*-positive Group

Endoscopic and histopathological findings		Yes (n=67)	Cag-A				Vac-A S1/S2 region				Vac-A M1/M2 region				
			No (n=27)				Yes (n=91)		No (n=3)		Yes (n=78)		No (n=16)		
		n	%	Sayı	%	p-value	n	%	Sayı	%	p-value	n	%	n	%	p-value
Gastric ulcer	No	61	91.0	26	96.3	**0.657**	84	92.3	3	100.0	1.000	72	92.3	15	93.8	**1.000**
	Yes	6	9.0	1	3.7		7	7.7	0	0.0		6	7.7	1	6.3	
Duodenal ulcer	No	53	79.1	26	96.3	**0.080**	77	84.6	2	66.7	0.970	67	85.9	12	75.0	**0.478**
	Yes	14	20.9	1	3.7		14	15.4	1	33.3		11	14.1	4	25.0	
Esophagitis	No	60	89.6	26	96.3	**0.515**	83	91.2	3	100.0	1.000	73	93.6	13	81.3	**0.212**
	Yes	7	10.4	1	3.7		8	8.8	0	0.0		5	6.4	3	18.8	
Antral nodularity	No	9	13.4	4	14.8	**0.418**	12	13.2	1	33.3	0.314	11	14.1	2	12.5	**0.717**
	Mild	7	10.4	6	22.2		12	13.2	1	33.3		11	14.1	2	12.5	
	Modarate	30	44.8	8	29.6		38	41.8	0	0.0		33	42.3	5	31.3	
	Severe	21	31.3	9	33.3		29	31.9	1	33.3		23	29.5	7	43.8	
Glandular atrophy	No-mild	53	79.1	24	88.9	**0.300**	74	81.3	3	100.0	1.000	63	80.8	14	87.5	**0.868**
	Moderate-severe	14	20.9	3	11.1		17	18.7	0	0.0		15	19.2	2	12.5	
Lymphoid aggregation	No-mild	30	44.8	12	44.4	**1.000**	41	45.1	1	33.3	1.000	37	47.4	5	31.3	**0.368**
	Moderate-severe	37	55.2	15	55.6		50	54.9	2	66.7		41	52.6	11	68.8	
Intestinal metaplasia	No	56	83.6	24	88.9	**0.739**	77	84.6	3	100.0	1.000	66	84.6	14	87.5	**1.000**
	Yes	11	16.4	3	11.1		14	15.4	0	0.0		12	15.4	2	12.5	
H. pylori density	No-mild	13	19.4	5	18.5	**0.691**	18	19.8	0	0.0	0.501	18	23.1	2	0.0	**0.071**
	Moderate-severe	54	80.6	22	81.5		73	80.2	3	100.0		60	76.9	14	100.0	

*p<0.05, **p<0.01, χ^2: Chi-square test, *H. pylori: Helicobacter pylori, Vac-A: Vacuolating cytotoxin A, Cag-A: Cytotoxin associated gene A*

DISCUSSION

Since *H. pylori* infection is usually acquired during childhood, it can cause chronic inflammation in the gastric mucosa and subsequently increase the risk of stomach cancer[1]. Nearly 50% of the world population is infected with this microorganism, and low socioeconomic status has been found to be one of the main predisposing factors associated with an increased risk of *H. pylori* infection[18-20]. In our study, low socioeconomic level was also a risk factor for contracting *H. pylori* infection (p=0.044). However, we did not find any association between *H. pylori* infection, living in urban/rural areas and choice of drinking water which suggests that living in rural areas is not associated with *H. pylori* infection.

In the pediatric age group, *H. pylori* gastritis is generally asymptomatic[19]. In our study, no statistical difference was found between the two groups in terms of the patients initial complaints (abdominal pain, retrosternal burning sensation and vomiting) (p>0.005).

As is known, *H. pylori* infection is associated with antral nodularity, erythematous and erosive gastritis, duodenal inflammation and ulcer in children, and can also be seen in the presence of mild gastritis or normal endoscopic findings[21,22]. Antral nodularity, which is the most important indicator of *H. pylori* infection in children has been reported at a rates of 69-91% in different countries, and the presence of antral nodularity has a sensitivity of

Table 4. Correlations between Cag-A and Vac-A S and M1/M2 region positivity, and endoscopic and histopathological findings in the *H. pylori*-positive Group

Variable	Coefficient	Cag-A protein positivity	Vac-A S region positivity	Vac-A M1/M2 region positivity
Cag-A protein	r	1	0.018	0.15
	p		0.86	0.148
Vac-A S region positivity	r	0.018	1	-0.082
	p	0.86		0.431
Vac-A M1/M2 region positivity	r	0.15	-0.082	1
	p	0.148	0.431	
Severity of gastritis	r	0.105	0.001	0.104
	p	0.315	0.99	0.32
Localisation	r	0.184	0.137	-0.071
	p	0.0.075	0.189	0.494
Gastritis type	r	0.094	0.027	0.067
	p	0.37	0.798	0.523
Duodenitis	r	0.071	-0.061	-0.057
	p	0.499	0.562	0.588
Gastric ulcer	r	0.091	0.052	0.021
	p	0.386	0.622	0.843
Duodenal ulcer	r	0.212*	-0.086	-0.112
	p	0.04	0.409	0.283
Presence of reflux	r	0.109	0.055	-0.166
	p	0.294	0.596	0.109
Antral nodularity	r	0.057	0.104	-0.072
	p	0.587	0.32	0.493
Chronic inflammation	r	0.202	-0.145	-0.044
	p	0.05	0.162	0.674
Activity	r	0.148	-0.001	-0.099
	p	0.154	0.994	0.342
Atrophy	r	0.089	0.084	0.072
	p	0.395	0.423	0.488
Lymphoid aggregation	r	-0.003	-0.041	-0.122
	p	0.977	0.692	0.24
Intestinal metaplasia	r	0.067	0.076	0.03
	p	0.518	0.467	0.771
H. pylori density	r	0.042	0.025	0.216*
	p	0.686	0.814	0.037

*p<0.05, **p<0.01, r: Correlation coefficient, *H. pylori: Helicobacter pylori, Vac-A: Vacuolating cytotoxin A, Cag-A: Cytotoxin associated gene A*

91.6% and a specificity of 91% for *H.pylori* infection[23-25]. In our study, we think that antral nodularity, with a rate of 87% in Group 1 and 60% in Group 2 detected during endoscopies performed by the same endoscopist, is an important indicator of *H. pylori*-positivity in children (p<0.001).

Studies have revealed that duodenal ulcers develop in 20% of people infected with *H. pylori* and can be asymptomatic even in children under 10 years of age. Incidence of peptic ulcer disease in children vary between 1.8% and 19.5%[26]. According to our results, the incidence rates of duodenal ulcer were 16% in the *H.*

Table 5. Comparison of endoscopic and histopathological findings according to *TLR9* gene 123T/C (rs5743836) polymorphisms in the *H. pylori*-positive group

Endoscopic and histopathological findings		TT (n=43)		TC (n=36)		CC (n=21)		
		n	%	n	%	n	%	p-value
Severity of gastritis	Normal-mild	12	27.9	12	33.3	9	42.9	0.495
	Moderate-severe	31	72.1	24	66.7	12	57.1	
Localization	Antrum-corpus	25	58.1	24	66.7	15	71.4	0.527
	Antrum	18	41.9	12	33.3	6	28.6	
Gastritis type	Normal	41	95.3	36	100.00	21	100.0	0.352
	Erythematous-erosive	2	4.7	0	0.0	0	0.0	
Duodenitis	No	24	55.8	13	36.1	14	66.7	0.059
	Yes	19	44.2	23	63.9	7	33.3	
Gastric ulcer	No	41	95.3	33	91.7	19	90.5	0.680
	Yes	2	4.7	3	8.3	2	9.5	
Duodenal ulcer	No	35	81.4	29	80.6	20	95.2	0.285
	Yes	8	18.6	7	19.4	1	4.8	
Esophagitis	No	36	83.7	35	97.2	18	85.7	0.160
	Yes	7	16.3	1	2.8	3	14.3	
Antral nodularity	No	2	4.7	7	19.4	4	19.0	0.391
	Mild	8	18.6	4	11.1	4	19.0	
	Moderate	17	39.5	16	44.4	7	33.3	
	Severe	16	37.2	9	25.0	6	28.6	
Chronic inflammation	Mild	11	25.6	9	25.0	4	19.0	0.493
	Modarate	29	67.4	21	58.3	16	76.2	
	Severe	3	7.0	6	16.7	1	4.8	
Activity	No	6	14.0	8	22.2	5	23.8	0.500
	Mild	11	25.6	13	36.1	5	23.8	
	Moderate	26	60.5	15	41.7	11	52.4	
Glandular atrophy	No	40	93.0	34	94.4	9	42.9	**p<0.001****
	Mild	0	0.0	1	2.8	5	23.8	
	Moderate	3	7.0	1	2.8	7	33.3	
Lymphoid aggregation	No-mild	21	48.80	19	52.80	6	28.60	0.199
	Moderate-severe	22	51.20	17	47.20	15	71.40	
Intestinal metaplasia	No	42	97.70	34	94.40	10	47.60	**p<0.001****
	Yes	1	2.30	2	5.60	11	52.40	
H. pylori density	Mild	7	16.30	6	16.70	6	28.60	0.413
	Moderate	32	74.40	27	75.00	11	52.40	
	Severe	4	9.30	3	8.30	4	19.00	

*p<0.05, **p<0.01, χ^2: Chi-square test, *H. pylori: Helicobacter pylori,* TLR: Toll-like receptor, TT: Homozygous for allele T, CC: Homozygous for allele C

pylori-positive and 5% in the *H. pylori*-negative group (p=0.021). Duodenal hyperemia and nodularity were observed in 49% of our patients (p = 0.002). In a study, *H. pylori* infection was reported in 92% of children with duodenal ulcer and 25% of children with peptic ulcer[27]. In our study, *H. pylori* was positive in 76.1% of children with duodenal ulcer and 50% of those with stomach ulcer. It is also known that the density of *H. pylori* in the antrum in children with *H. pylori* infection is significantly lower than in adults, and this is one of the reasons why gastric ulcers are less common than duodenal ulcers in children[27].

Table 6. Correlations between *TLR9* gene 123T/C (rs5743836) polymorphisms, glandular atrophy and intestinal metaplasia in *H. pylori*-positive group

Model	Estimated variable	B	S.E.	p-value	Exp(B)/odds ratio	CIs 95% CI for Exp(B)	
						Lower	Upper
Intestinal metaplasia	*TLR9* gene			**0.000**			
	TLR9 (TC)	0.90	1.25	0.468	2.47	0.22	28.42
	TLR9 (CC)	3.83	1.10	**0.001**	46.20	5.33	400.67
	Constant	-3.74	1.01	**0.000**	0.02		
Glandular atrophy	*TLR9* gene			**0.000**			
	TLR9 (TC)	-0.24	0.94	0.797	0.78	0.12	4.97
	TLR9 (CC)	2.88	0.74	**0.000**	17.78	4.14	76.34
	Constant	-2.59	0.60	**0.000**	0.08		

Dependent variable: Intestinal metaplasia and atrophy, Exp(B): Odds ratio, CI: Confidence interval, S.E.: Standard error, TLR: Toll-like receptor, AA: Homozygous for allele A, AG: Heterozygous, CC: Homozygous for allele C

H. pylori infection is the most common cause of chronic superficial gastritis. Atrophic gastritis, intestinal metaplasia and dysplasia, and finally gastric adenocarcinoma may develop after chronic gastritis in cases with *H. pylori* infection. These disease stages evolve very slowly and can stop at any stage[26,27]. Gastric inflammation in children may not demonstrate obvious pathological changes as in adults, or the transition between stages may be very slow. Therefore, different publications report different rates of chronic inflammation, atrophy or intestinal metaplasia in cases with *H. pylori* infection. While moderate to severe chronic inflammation was reported in 65.8-68.2% of these cases, we found its incidence as 76% in our study[28,29].

Although gastric atrophy, also defined as glandular tissue loss, is not as common in children as in adults, it can develop secondary to *H. pylori* infection. Chronic gastritis in adults is often accompanied by intestinal metaplasia, and its incidence increases with the duration of the disease. In studies conducted in different countries, various incidence rates have been reported for gastric atrophy (Tunisia: 9.3%; USA: 52.6%; Japan: 51.7%, and Taiwan: 30.4) and intestinal metaplasia (USA: 15.7%; and Japan: 4.6%)[30-33]. In studies conducted in Turkey, the rates of gastric atrophy and intestinal metaplasia were reported as 2.2% and 1.1% by Usta et al.[34] and 2.5% and 0% by Tutar et al.[35]. In summary, based on our results, consistent with the literature data, in *H. pylori*-positive cases gastric atrophy, and intestinal metaplasia were detected in 17% and 14% of the cases, respectively. Gastric atrophy in children is often found in the antrum or antrum corpus region[36,37]. For this reason, when performing endoscopic biopsies, care was taken to take two biopsy specimens from the antral region in all patients.

The prevalence rates of Cag-A positivity in isolated *H. pylori* strains, and their relationship with GI diseases varied widely in different parts of the world[38]. While the Cag-A positivity rates in Europe and the USA generally vary between 60-70%, almost all *H. pylori* strains in East Asian countries are Cag-A (+)[39,40]. In studies conducted in Asian countries, different prevalence rates of Cag-A in isolated *H. pylori* strains have been reported (India: 96%; China: 86%; Bangladesh: 95%, and Iran: 77%)[41-44]. Ghasemi et al.[45] found a Cag-A positivity rate of 85% in their study performed in Iran and reported that presence of Cag-A positivity was associated with peptic ulcer. Podzorski et al.[46] found that 66% of 61 strains isolated in their study performed in the USA were Cag-A(+). Similarly, Gatti et al.[47] reported that 73.4% of 95 *H. pylori* strains isolated in their study carried out in Brazil were Cag-A (+). The prevalence of Cag-A in Europe shows a profile similar to that reported for the USA. Cag-A positivity rates were reported as 66%, and 68% in studies carried out in Spain and in England, respectively[48,49]. In this study, 67 (71.2%) of 94 *H. pylori* strains demonstrated Cag-A (+). There was a low positive correlation between Cag-A positivity rates and the presence of duodenal ulcer (p=0.04). These results have shown that the rates of duodenal ulcers would increase in parallel with an increse in the levels of Cag-A protein. In various studies conducted in Turkey, Cag-A positivity and prevalence have been reported to vary between 65, and 80%, and it has been suggested that the presence of Cag-A is associated with peptic ulcer and duodenal ulcer[50,51]. There are publications in the literature showing that prepyloric duct ulcers are

more prominent in many single-center pediatric patient groups, especially in cases of duodenal ulcer and severe antral gastritis, and in cases infected with Cag-A positive bacteria[45,50-52].

Although all *H. pylori* strains have the *Vac-A* gene, only 50% of them produce active Vac-A toxin[53]. The *Vac-A* gene contains a signal (s) and a middle (m) region, which show significant sequence diversities among strains. It has been reported that S1/M1 genotypes show greater cytotoxic activity *in vitro* and are more frequently associated with peptic ulcer disease[53]. There are also differences in Vac-A genotypes between countries or regions. In a study conducted on 119 children in Portugal, it was stated that only Vac-A S2 caused less severe inflammation in clinical and histopathological terms[54]. None of the Vac-A genotypes extracted from *H. pylori* strains obtained from 33 Korean children were associated with neutrophil activity or chronic inflammation[55]. In a study conducted in Slovakia, a statistically significant relationship was detected between high bacterial infiltration and chronic inflammation in Vac-A S1-positive samples, but no relationship could be established with precancerous lesions such as antral atrophy and intestinal metaplasia[56]. One limitation of this study is that we were not able to examine both the s- and m-domain subclasses of Vac-A. However, a low positive correlation was found between the presence of Vac-A M1 in the *H. pylori*-positive group ($p<0.05$). It was observed that the density of *H. pylori* in the tissue would increase with the presence of the Vac-A M1/M2 region.

H. pylori infection increases the expressions of TLR 2, 4, 5, and 9 in the gastric mucosa and the number of epithelial cells expressing IL-8, IL-10, and tumor necrosis factor-alpha[57]. Twelve different mutations in TLR4 have been described in the literature. It has been demonstrated that TLR4 Asp299Gly polymorphism disrupts the normal structure of the extracellular domain of TLR4 with the potential of reducing susceptibility to *H. pylori* by weakening the binding affinity of bacterial ligands to the TLR4 receptor A>G. *H. pylori* passes through the extracellular space and causes an exaggerated inflammatory response with serious tissue damage[58-60]. As a result, *H. pylori* colonization accelerates the development of severe inflammation, hypochlorhydria and gastric atrophy[59]. It is stated that the presence of G allele is the responsible risk factor in this process of mutation[60]. However, conflicting results have been reported by researchers in clinical studies. Studies conducted on adult patients do not associate TLR4 Asp299Gly polymorphism with gastritis, duodenal ulcer and stomach cancer[61-65]. Some studies suggest that TLR4 Asp299Gly carriage significantly affects the occurrence of chronic gastritis and peptic ulcer disease, causing atrophy and intestinal metaplasia[66-69]. According to our results, only 6 patients in the *H-pylori*-positive group were heterozygous carriers of the TLR4Asp299Gly (rs4986790) polymorphism and no relationship was found between this mutation and *H. pylori*-positivity. Therefore, statistical evaluation could not be made. Similarly, in a study conducted in pediatric cases, it was found that TLR4 Asp299Gly polymorphism was not associated with *H. pylori*-positivity[70].

Expression of TLR9, an endosomal sensor of unmethylated CpG-rich DNA motifs, increases when the gastric epithelium is infected with *H. pylori*, leading to stimulation of T helper 1 monocytes and increased activation of macrophages[71-73]. In an *in vitro* mouse experiment, TLR 9 expression was found to be 4 times higher in tissues infected with *H. pylori*[74]. TLR91237 TC (rs5743836) polymorphism further worsens this inflammation and predisposes the patient to neoplastic complications with chronic infection in the presence of the C allele[75]. The TLR9-1237 TC (rs5743836) SNP is located in the promoter region. An in silico study found that the C variant allele creates an alternative NF-κB binding site, which may be functionally relevant. Presumably this process increases transcriptional activation by TLR9 and potentially exacerbates the inflammatory reaction by affecting CpG DNA activation of pro-inflammatory cytokines[17]. In addition, functional studies have shown that individuals carrying the C variant allele have significantly higher luciferase activity, by demonstrating modulation of TLR9 transcriptional activity by rs5743836[17].

The TLR9 1237, TC+CC or CC genotype has been associated with a higher risk of gastric cancer than the C genotype [recessive odds ratio (OR) =5.01, 95% confidence interval (CI): 2.52 to 9.94, $p<0.0001$] in chronic gastritis (recessive OR =4.63; 95% CI: 2.44 to 8.79, $p<0.0001$) groups[76]. Another study conducted in an Asian population found no link between *H. pylori* infection and the risk of developing gastric cancer[77]. A study performed in a Mexican population found that the 1237C allele of TLR9 was more commonly detected in patients with metaplasia (19.35%) than in patients with gastritis (15.63%), cancer (15.93%), or duodenal ulcer (12.82%). However, the differences in incidence rates were not statistically significant[78].

CONCLUSION

Based on litearture data the TLR9 1237T/C polymorphism has not been reported in the pediatric age group. According to our results, patients with CC polymorphism had moderate/severe glandular atrophy (57.1%) and intestinal metaplasia (52.4%). The higher rates of glandular atrophy and intestinal metaplasia in patients with the CC polymorphism compared to patients with the TT and TC polymorphisms suggest that the likelihood of cancer in patients carrying this allele increases, especially in developing countries where exposure to *H. pylori* is higher starting from a young age. We attributed the high incidence of intestinal metaplasia and glandular atrophy in children carrying the CC polymorphism to the fact that this study was conducted in only one province of Turkey with a small group of cases. Large case scans and even the identification of the rs5743836 TLR9 minor C allele in different ethnic populations may provide a better identification of the individuals who are more susceptible to critically serious complications of chronic *H. pylori* infection and therefore may require strict endoscopic surveillance more frequently.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee of the Manisa Celal Bayar University (approval number: 27, date: 17.03.2012).

Informed Consent: When the patients came for their routine polyclinic check-ups after their treatment was achieved based on their established diagnoses, written information, and consent forms were given to their parents to be read, and signed by them voluntarily if they approved the conduction of the study.

Author Contributions

Surgical and Medical Practices: A.C.T., H.E.K., Concept: H.E.K., Design: H.E.K., Data Collection and Processing: A.C.T., Analysis and Interpretation: A.C.T., H.G., H.O., F.Ö., S.A., Literature Search: A.C.T., Writing: A.C.T.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Kusters JG, van Vliet AH, Kuipers EJ. Pathogenesis of *Helicobacter pylori* infection. Clin Microbiol Rev. 2006;19(3):449-90. doi: 10.1128/CMR.00054-05
2. Pandey R, Misra V, Misra S, Dwivedi M, Kumar A,Tiwari BK. *Helicobacter pylori* and gastric cancer. Asian Pac J Cancer Prev. 2010;11(3):583-8.
3. El-Omar EM, K Oien, LS Murray, A El-Nujumi, A Wirz, D Gillen, et al. Increased prevalence of precancerous changes in relatives of gastric cancer patients: critical role of *Helicobacter pylori.* Gastroenterology. 2000;118(1):22-30. doi: 10.1016/s0016-5085(00)70410-0
4. Bagheri N, Taghikhani A, Rahimian G, Salimzadeh L, Azadegan Dehkordi F, Zandi F, et al. Association between virulence factors of *Helicobacter pylori* and gastric mucosal interleukin-18 mRNA expression in dyspeptic patients. Microb Pathog. 2013;65:7-13. doi: 10.1016/j.micpath.2013.08.005
5. Chang WL, Yeh YC, Sheu BS. The impacts of *H. pylori* virulence factors on the development of gastroduodenal diseases. J Biomed Sci. 2018;25(1):68. doi: 10.1186/s12929-018-0466-9
6. Kao CY, Sheu BS, Wu JJ. *Helicobacter pylori* infection: an overview of bacterial virulence factors and pathogenesis. Biomed J. 2016;39(1):14-23. doi: 10.1016/j.bj.2015.06.002
7. Foegeding NJ, Caston RR, McClain MS, Ohi MD, Cover TL. An overview of *Helicobacter pylori* VacA toxin biology. Toxins (Basel). 2016;8(6):173. doi: 10.3390/toxins8060173
8. Conteduca V, Sansonno D, Lauletta G, Russi S, Ingravallo G, Dammacco F. *H. pylori* infection and gastric cancer: state of the art. Int J Oncol. 2013;42(1):5–18. doi: 10.1128/CMR.00054-05
9. Yong X, Tang B, Li BS, Xie R, Hu CJ, Luo G, et al. *Helicobacter pylori* virulence factor CagA promotes tumorigenesis of gastric cancer via multiple signaling pathways. Cell Commun Signal. 2015;13:30. doi: 10.1186/s12964-015-0111-0
10. Barton GM, Medzhitov R. Toll-like receptor signaling pathways. Science. 2003;300(5625):1524-5. doi: 10.1126/science.1085536
11. Schmausser B, Andrulis M, Endrich S, Lee SK, Josenhans C, Muller-Hermelink HK, et al. Expression and subcellular distribution of tolllike receptors TLR4, TLR5 and TLR9 on the gastric epithelium in *Helicobacter pylori* infection. Clin Exp Immunol. 2004;136(3):521-6. doi: 10.1111/j.1365-2249.2004.02464.x
12. Ishihara S, Rumi MA, Kadowaki Y, Ortega-Cava CF, Yuki T, Yoshino N, et al. Essential role of MD-2 in TLR4-dependent signaling during *Helicobacter pylori*-associated gastritis. J Immunol. 2004;173(2): 1406-16. doi: 10.4049/jimmunol.173.2.1406
13. Kawahara T, Kuwano Y, Teshima-Kondo S, Kawai T, Nikawa T, Kishi K, et al. Toll-like receptor 4 regulates gastric pit cell responses to *Helicobacter pylori* infection. J Med Invest. 2001;48(3-4):190-7.
14. Latz E, A Schoenemeyer, A Visintin, KA Fitzgerald, BG Monks, CF Knetter, et al. TLR9 signals after translocating from the ER to CpG DNA in the lysosome. Nat Immunol. 2004;5(2):190-8. doi: 10.1038/ni1028
15. de Oliveira JG, Silva AE. Polymorphisms of the TLR2 and TLR4 genes are associated with risk of gastric cancer in a Brazilian population. World J Gastroenterol. 2012;18(11):1235-42. doi: 10.3748/wjg.v18.i11.1235
16. Arbour NC, Lorenz E, Schutte BC, Zabner J, Kline JN, Jones M, et al. TLR4 mutations are associated with endotoxin hyporesponsiveness in humans. Nat Genet. 2000;25(2):187-91. doi: 10.1038/76048

17. Ng MT, Van't Hof R, Crockett JC, Hope ME, Berry S, Thomson J, et al. Increase in NF-kappaB binding affinity of the variant C allele of the toll-like receptor 9 1237T/C polymorphism is associated with *Helicobacter pylori*-induced gastric disease. Infect Immun. 2010;78(3):1345-52. doi: 10.1128/IAI.01226-09

18. McColl KE. Clinical practice. *Helicobacter pylori* infection. N Engl J Med. 2010;362(17):1597-604. doi: 10.1056/NEJMcp1001110

19. McCallion WA, Murray LJ, Bailie AG, Dalzell AM, O'Reilly DP, Bamford KB. *Helicobacter pylori* infection in children: relation with current household living conditions. Gut. 1996;39(1):18-21. doi: 10.1136/gut.39.1.18

20. Altuğlu I, Sayiner AA, Ozacar T, Egemen A, Bilgiç A. Seroprevalence of *Helicobacter pylori* in a pediatric population. Turk J Pediatr. 2001;43(2):125-7.

21. Iwanczak B, Laszewicz W, Iwanczak F, Dzierzanowska-Fangrat K, Rozynek M, Dzierzanowska D, et al. Genotypic and clinical differences of seropositive *Helicobacter pylori* children and adults in the Polish population. J Physiol Pharmacol. 2014;6:801-7.

22. Kato S, Nishino Y, Ozawa K, Konno M, Maisawa S, Toyoda S, et al. The prevalence of *Helicobacter pylori* in Japanese children with gastritis or peptic ulcer disease. J Gastroenterol. 2004;39(8):734-8. doi: 10.1007/s00535-004-1381-2

23. Bujanover Y, Konikoff F, Baratz M. Nodular gastritis and *Helicobacter pylori*. J Pediatr Gastroenterol Nutr. 1990;11:41-4. doi: 10.1097/00005176-199007000-00008

24. Elitsur Y, Raghuverra A, Sadat T, Vaid P. Is gastric nodularity a sign for gastric inflammation associated with *Helicobacter pylori* infection in children? J Clin Gastroenterol. 2000;30(3):286-8. doi: 10.1097/00004836-200004000-00016

25. Łazowska-Przeorek I, Kotowska M, Banasiuk M, Karolewska-Bochenek K, Banaszkiewicz A, Gawrońska A, et al. Value of antral nodularity for the diagnosis of *Helicobacter pylori* infection in children. Med Sci Monit. 2015;21:1827-30. doi: 10.12659/MSM.893467

26. Pacifico L, Anania C, Osborn JF, Ferraro F, Chiesa C. Consequences of *Helicobacter pylori* infection in children. World J Gastroenterol. 2010;16(41):5181-94. doi: 10.3748/wjg.v16.i41.5181

27. Rowland M, Bourke B, Drumm B. *Helicobacter pylori* and peptic ulcer disease. In: Walker's Pediatric Gastrointestinal Disease, Kleinman RE, Goulet OJ, Sanderson IR, Sherman PM, Shneider P, Vergani GM (eds). Hamilton BC Decker Inc.; 2008. p. 140-151.

28. Cohen MC, Cueto Rúa E, Balcarce N, Drut R. Sulfomucins in *Helicobacter pylori*-associated chronic gastritis in children: is this incipient intestinal metaplasia? J Pediatr Gastroenterol Nutr. 2000;31(1):63-7. doi: 10.1097/00005176-200007000-00014

29. Langner M, Machado RS, Patrício FR, Kawakami E. Evaluation of gastric histology in children and adolescents with *Helicobacter pylori* gastritis using the Update Sydney System. Arq Gastroenterol. 2009;46(4):328-32. doi: 10.1590/s0004-28032009000400015

30. Boukthir S, Mrad SM, Kalach N, Sammoud A. Gastric atrophy and *Helicobacter pylori* infection in children.Trop Gastroenterol. 2009;30(2):107-9.

31. Guarner J, Herrera-Goepfert R, Mohar A, Sanchez L, Halperin D, Ley C, et al. Interobserver variability in application of the revised Sydney classification for gastritis. Hum Pathol. 1999;30(12):1431-4. doi: 10.1016/s0046-8177(99)90164-8

32. Kato S, Nakajima S, Nishino Y, Ozawa K, Minoura T, Konno M, et al. Association between gastric atrophy and *Helicobacter pylori* infection in Japanese children: a retrospective multicenter study. Dig Dis Sci. 2006;51:99-104. doi: 10.1007/s10620-006-3091-5

33. Hsieh H, Yang HB, Sheu BS, Yang YJ. Atrophic gastritis in *Helicobacter pylori*-infected children. Helicobacter. 2022;27(3):12885. doi: 10.1111/hel.12885

34. Usta Y, Saltk-Temizel IN, Ozen H. Gastric atrophy and intestinal metaplasia in *Helicobacter pylori* infection. J Pediatr Gastroenterol Nutr. 2004;38(5):548. doi: 10.1097/00005176-200405000-00018

35. Tutar E, Ertem D, Kotiloğlu KE, Pehlivanoğlu E. Endoscopic and histopathologic findings associated with *H. pylori* infection in very young children. Dig Dis Sci. 2009;54(1):111-7. doi: 10.1007/s10620-008-0334-7

36. Ricuarte O, Gutierrez O, Cardona H, Kim JG, Graham DY, El-Zimaity HM. Atrophic gastritis in young children and adolescents. J Clin Pathol. 2005;58(11):1189-93. doi: 10.1136/jcp.2005.026310

37. Dixon MF, Genta RM, Yardley JH, Correa P. Classification and grading of gastritis. The updated Sydney system. International workshop on the histopathology of gastritis, Houston 1994. Am J Surg Pathol. 1996;20:1161-81. doi: 10.1097/00000478-199610000-00001

38. Achtman M, Azuma T, Berg DE, Ito Y, Morelli G, Pan ZJ, et al. Recombination and clonal groupings within *Helicobacter pylori* from different geographical regions. Mol Microbiol. 1999;32(3):459-70. doi: 10.1046/j.1365-2958.1999.01382.x

39. Kim SY, Woo CW, Lee YM, Son BR, Kim JW, Chae HB, et al. Genotyping CagA, VacA subtype, IceA1, and BabA of *Helicobacter pylori* isolates from Korean patients, and their association with gastroduodenal diseases. J Korean Med Sci. 2001;16(5):579-84. doi: 10.3346/jkms.2001.16.5.579

40. Maeda S, Ogura K, Yoshida H, Kanai F, Ikenoue T, Kato N, et al. Major virulence factors, VacA and CagA, are commonly positive in *Helicobacter pylori* isolates in Japan. Gut. 1998;42(3):338-43. doi: 10.1136/gut.42.3.338

41. Arachchi HS, Kalra V, Lal B, Bhatia V, Baba CS, Chakravarthy S, et al. Prevalence of duodenal ulcer-promoting gene (dupA) of *Helicobacter pylori* in patients with duodenal ulcer in North Indian population. Helicobacter. 2007;12(6):591-7. doi: 10.1111/j.1523-5378.2007.00557.x

42. Qiao W, Hu JL, Xiao B, Wu KC, Peng DR, Atherton JC, et al. cagA and vacA genotype of *Helicobacter pylori* associated with gastric diseases in Xi'an area. World J Gastroenterol. 2003;9(8):1762-66. doi: 10.3748/wjg.v9.i8.1762

43. Sarker SA, Nahar S, Rahman M, Bardhan PK, Nair GB, Beglinger C, et al. High prevalence of cagA and vacA seropositivity in asymptomatic Bangladeshi children with *Helicobacter pylori* infection. Acta Paediatr. 2004;93(11):1432-6. doi: 10.1080/08035250410033088

44. Kamali-Sarvestani E, Bazargani A, Masoudian M, Lankarani K, Taghavi AR, Saberifiroozi M. Association of *H. pylori* cagA and vacA genotypes and *IL-8* gene polymorphisms with clinical outcome of infection in Iranian patients with gastrointestinal

diseases. World J Gastroenterol. 2006;12(32):5205-10. doi: 10.3748/wjg.v12.i32.5205

45. Ghasemi A, Shirazi MH, Ranjbar R, Khorramizadeh MR, Daryani NE, Hosseini M. The prevalence of *cagA* and *cagE* genes in *Helicobacter pylori* strains isolated from different patient groups by polymerase chain reaction. Pak J Biol Sci. 2008;11(22):2579-83. doi: 10.3923/pjbs.2008.2579.2583
46. Podzorski RP, Podzorski DS, Wuerth A, Tolia V. Analysis of the *vacA, cagA, cagE, iceA,* and *babA2* genes in *Helicobacter pylori* from sixty-one pediatric patients from the Midwestern United States. Diagn Microbiol Infect Dis. 2003;46(2):83-8. doi: 10.1016/s0732-8893(03)00034-8
47. Gatti LL, Modena JL, Payao SL, Smith Mde A, Fukuhara Y, de Oliveira RB, et al. Prevalence of *Helicobacter pylori* cagA, iceA and babA2 alleles in Brazilian patients with upper gastrointestinal diseases. Acta Trop. 2006;100(3):232-40. doi: 10.1016/j.actatropica.2006.08.014
48. Alarcon T, Domingo D, Martinez MJ, Lopez-Brea M. *cagA* gene and vacA alleles in Spanish *Helicobacter pylori* clinical isolates from patients of different ages. FEMS Immunol Med Microbiol. 1999;24(2):215-9. doi: 10.1111/j.1574-695X.1999.tb01285.x
49. Warburton VJ, Everett S, Mapstone NP, Axon AT, Hawkey P, Dixon MF. Clinical and histological associations of cagA and vacA genotypes in *Helicobacter pylori* gastritis. J Clin Pathol. 1998;51(1):55-61. doi: 10.1136/jcp.51.1.55. PMID: 9577374
50. Salih BA, Abasiyanik MF, Ahmed N. A preliminary study on the genetic profile of cag pathogenicity-island and other virulent gene loci of *Helicobacter pylori* strains from Turkey. Infect Genet Evol. 2007;7(4):509-12. doi: 10.1016/j.meegid.2007.03.002
51. Kantarçeken B, Murat A, Esin A, Fatih K, H, MM, Hakan H, et al. Association of CagA and VacA presence with ulcer and non-ulcer dyspepsia in a Turkish population. World J Gastroenterol. 2003;9(7):1580-3. doi: 10.3748/wjg.v9.i7.1580
52. Saribasak H, Salih BA, Yamaoka Y, Sander E. Analysis of *Helicobacter pylori* genotypes and correlation with clinical outcome in Turkey. J Clin Microbiol. 2004;42(4):1648-1651. doi: 10.1128/JCM.42.4.1648-51.2004
53. Keikha M, Ali-Hassanzadeh M, Karbalaei M. Association of *Helicobacter pylori* vacA genotypes and peptic ulcer in Iranian population: a systematic review and meta-analysis. BMC Gastroenterol. 2020;20(1):266. doi: 10.1186/s12876-020-01406-9
54. Lopes AI, Palha A, Monteiro L, Olcastro M, Pelerito A, Fernandes A. *Helicobacter pylori* genotypes in children from a population at high gastric cancer risk: no association with gastroduodenal histopathology. Am J Gastroenterol. 2006;101(9):2113-22. doi: 10.1111/j.1572-0241.2006.00732.x
55. Ko JS, Kim KM, Oh YL, Seo JK. cagA, vacA genotypes of *Helicobacter pylori* in gastric cancer patients: relation with histological changes and clinical outcomes. J Clin Pathol. 2003;56(9):696-700. doi: 10.1136/jclinpath.56.9.696
56. Homan M, Luzar B, Kocjan BJ, Orel R, Mocilnik T, Shrestha M, et al. Prevalence and clinical relevance of cagA, vacA, and iceA genotypes of *Helicobacter pylori* isolated from Slovenian children. Am J Gastroenterol. 2006;101(9):2113-22. doi: 10.1097/MPG.0b013e31818f09f2
57. Lagunes-Servin H, Torres J, Maldonado-Bernal C, Pérez-Rodríguez M, Huerta-Yépez S, Madrazo de la Garza A, et al. Toll-like receptors and cytokines are upregulated during *Helicobacter pylori* infection in children. Helicobacter. 2013;18(6):423-32. doi: 10.1111/hel.12067
58. Xu D, Komai-Koma M, Liew FY. Expression and function of toll-like receptor on T cells. Cell Immunol. 2005;233(2):85-9. doi: 10.1016/j.cellimm.2005.04.019
59. Sanduleanu S, Jonkers D, De Bruïne A, Hameeteman W, Stockbrügger RW. Double gastric infection with *Helicobacter pylori* and non-*Helicobacter pylori* bacteria during acid-suppressive therapy: increase of proinflammatory cytokines and development of atrophic gastritis. Aliment Pharmacol Ther. 2001;15(8):1163-75. doi: 10.1046/j.1365-2036.2001.01029.x
60. Hellmig S, Fischbach W, Goebeler-Kolve ME, Folsch UR, Hampe J, Schreiber S. Association study of a functional Toll-like receptor 4 polymorphism with susceptibility to gastric mucosa-associated lymphoid tissue lymphoma. Leuk Lymphoma. 2005;46(6):869. doi:10.1080/1042819050086451
61. Garza Gonzalez E, Bosques-Padilla FJ, Mendoza-Ibarra SI, Flores-Gutierrez JP, Maldonado-Garza HJ, Perez-Perez GI. Assessment of the Toll-like receptor 4 Asp299Gly, Thr399Ile and interleukin-8 -251 polymorphisms in the risk for the development of distal gastric cancer. BMC Cancer. 2007;7:70. doi: 10.1186/1471-2407-7-70
62. Kato I, Canzian F, Plummer M, Franceschi S, Doorn L-J, Vivas J, et al. Polymorphisms in genes related to bacterial lipopolysaccharide/peptidoglycan signaling and gastric precancerous lesions in a population at high risk for gastric cancer. Dig Dis Sci. 2007;52(1):254-61. doi: 10.1007/s10620-006-9303-1
63. Wu MS, Cheng TY, Shun CT, Lin MT, Chen LC, Lin JT. Functional polymorphisms of CD14 and Toll-like receptor 4 in Taiwanese Chinese with *Helicobacter pylori*-related gastric malignancies. Hepatogastroenterology. 2006;53(71):807-10.
64. Hofner P, Gyulai Z, Kiss ZF, Tiszai A, Tiszlavicz L, Toth G, et al. Genetic polymorphisms of NOD1 and IL-8, but not polymorphisms of *TLR4* genes are associated with *Helicobacter pylori*-induced duodenal ulcer and gastritis. Helicobacter. 2007;12(2):124. doi: 10.1111/j.1523-5378.2007.00481.x
65. Mirkamandar E, Nemati M, Hayatbakhsh MM, Bassagh A, Khosravimashizi A, Jafarzadeh A. Association of a single nucleotide polymorphism in the *TLR2* gene (rs3804099), but not in the *TLR4* gene (rs4986790), with *Helicobacter pylori* infection and peptic ulcer. Turk J Gastroenterol. 2018;29(3):283-91. doi: 10.5152/tjg.2018.17484
66. Hold GL, Rabkin CS, Chow WH, Smith MG, Gammon MD, Risch HA, et al. A functional polymorphism of *toll-like receptor 4* gene increases risk of gastric carcinoma and its precursors. Gastroenterology. 2007;132:905-12. doi: 10.1053/j.gastro.2006.12.026
67. Achyut BR, Ghoshal UC, Moorchung N, Mittal B. Association of *Toll-like receptor-4 (Asp299Gly and Thr399Ileu)* gene polymorphisms with gastritis and precancerous lesions. Hum Immunol. 2007;68(11):901-7. doi: 10.1016/j.humimm.2007.10.006
68. Eed EM, Hawash YA, Khalifa AS, Alsharif KF, Alghamdi SA, Almalki AA, et al. Association of *Toll-Like Receptors 2, 4,*

9 and *10* genes polymorphisms and *Helicobacter pylori*-related gastric diseases in Saudi patients. Indian Journal of Medical Microbiology. 2020;38(1):94–100. doi: 10.4103/ijmm.IJMM_20_164

69. Loganathan R, Nazeer M, Goda V, Devaraju P, Ali M, Karunakaran P, et al. Genetic variants of *TLR4* and *TLR9* are risk factors for chronic *Helicobacter pylori* infection in South Indian Tamils. Human Immunology. 2017;78(2):216-20. doi: 10.1016/j.humimm.2016.12.002
70. Meliţ LE, Mărginean CO, Bănescu C, Bogliş A, Mocan S, Iancu M. The relationship between *TLR4 rs4986790* and *rs4986791* gene polymorphisms and *Helicobacter pylori* infection in children with gastritis. M Pathol Res Pract. 2019 Dec;215(12):152692. doi: 10.1016/j.prp.2019.152692
71. Belmont L, Rabbe N, Antoine M, Cathelin D, Guignabert C, Kurie J, et al. Expression of TLR9 in tumor-infiltrating mononuclear cells enhances angiogenesis and is associated with a worse survival in lung cancer. Int J Cancer. 2014;134:765-77. doi: 10.1002/ijc.28413
72. Zambirinis CP, Levie E, Nguy S, Avanzi A, Barilla R, Xu Y, et al. TLR9 ligation in pancreatic stellate cells promotes tumorigenesis. J Exp Med. 2015;212:2077-94. doi: 10.1084/jem.20142162
73. Ilvesaro JM, Merrell MA, Li L, Wakchoure S, Graves D, Brooks S, et al. Toll-like receptor 9 mediates CpG oligonucleotide-induced cellular invasion. Mol Cancer Res. 2008;6:1534-43. doi: 10.1158/1541-7786.MCR-07-2005
74. Tang K, McLeod L, Livis T, West AC, Dawson R, Yu L, et al. Toll-like receptor 9 promotes ınitiation of gastric tumorigenesis by augmenting inflammation and cellular proliferation. BJ Cell Mol Gastroenterol Hepatol. 2022;14(3):567-86. doi: 10.1016/j.jcmgh.2022.06.002
75. Ding L, Chakrabarti J, Sheriff S, Li Q, Thi Hong HN, Sontz RA, et al. Toll-like receptor 9 pathway mediates schlafen+-MDSC polarization during *Helicobacter*-induced gastric metaplasias. Gastroenterology. 2022;163(2):411-25.e4. doi: 10.1053/j.gastro.2022.04.031
76. Susi MD, Lourenço Caroline M, Rasmussen LT, Payão SLM, Rossi AFT, et al. Toll-like receptor 9 polymorphisms and *Helicobacter pylori* influence gene expression and risk of gastric carcinogenesis in the Brazilian population. World J Gastrointest Oncol. 2019;11(11):998-1010. doi: 10.4251/wjgo.v11.i11.998
77. Wang X, Xue L, Yang Y, Xu L, Zhang G. TLR9 promoter polymorphism is associated with both an increased susceptibility to gastric carcinoma and poor prognosis. PLoS One. 2013;8: e65731. doi: 10.1371/journal.pone.0065731
78. Trejo-de la O A, Torres J, Sánchez-Zauco N, Pérez-Rodríguez M, Camorlinga-Ponce M, Flores-Luna L, et al. Polymorphisms in TLR9 but not in TLR5 increase the risk for duodenal ulcer and alter cytokine expression in the gastric mucosa. Innate Immun. 2015;21:706-13. doi: 10.1177/1753425915587130

DOI: 10.4274/jbuch.galenos.2024.39112
J Dr Behcet Uz Child Hosp 2024;14(3):195-198

Case Report

A Case with Autism Spectrum Disorder and Concomitant Arginase Deficiency

Otizm Spektrum Bozukluğu ve Arjinaz Eksikliği Birlikteliği Olan Olgu

Rabia Eren[1], Buket Canlan Özaydın[2], Emine Göksoy[3], Zehra Manav Yiğit[4], Börte Gürbüz Özgür[1]

[1]Aydın Adnan Menderes University Faculty of Medicine, Department of Child and Adolescent Psychiatry, Aydın, Turkey
[2]University of Health Sciences Turkey, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital, Department of Child and Adolescent Psychiatry, İzmir, Turkey
[3]Aydın Adnan Menderes University Faculty of Medicine, Department of Pediatrics, Division of Pediatric Metabolism, Aydın, Turkey
[4]Aydın Adnan Menderes University Faculty of Medicine, Department of Medical Genetics, Aydın, Turkey

ABSTRACT

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by lack of social interaction, limited areas of interest, and repetitive behaviors. Comprehensive screening studies have shown that the prevalence of ASD is increasing. Arginase deficiency is an autosomal recessive metabolic disorder that affects the last step of the urea cycle. In this report, clinical features, neurological findings and genetic analysis results of an 11-year-old boy diagnosed with ASD have been discussed. Additionally, accompanying late diagnosed arginase deficiency has been also highlighted. In addition to the coexistence of ASD and metabolic diseases, the importance of early diagnosis and treatment in such cases has been emphasized.

Keywords: Arginase deficiency disorder, autism spectrum disorder, inborn errors of metabolism, neurodevelopmental disorders

ÖZ

Otizm spektrum bozukluğu (OSB), sosyal etkileşim eksikliği, sınırlı ilgi alanları ve tekrarlayan davranışlarla karakterize edilen bir nörogelişimsel bozukluktur. Kapsamlı tarama çalışmaları, OSB'nin prevalansının arttığını göstermektedir. Arginaz eksikliği, üre döngüsünün son basamağını etkileyen otozomal resesif geçişli bir metabolik hastalıktır. Bu makalede OSB tanısı alan 11 yaşındaki bir erkek çocuğun klinik özellikleri, nörolojik bulguları ve genetik analiz sonuçları tartışılmıştır. Ayrıca, geç tanı konulan arginaz eksikliğine de vurgu yapılmıştır. Otizm ile metabolik hastalıkların birlikte görülmesinin yanı sıra, bu tür olgularda erken tanı ve tedavinin önemi vurgulanmıştır.

Anahtar kelimeler: Arginaz eksikliği hastalığı, otizm spektrum bozukluğu, doğuştan metabolizma hataları, nörogelişimsel bozukluklar

Received: 17.09.2024
Accepted: 08.10.2024

Corresponding Author
Börte Gürbüz Özgür,
Aydın Adnan Menderes University Faculty of Medicine, Department of Child and Adolescent Psychiatry, Aydın, Turkey
borte.gurbuz@adu.edu.tr
ORCID: 0000-0002-9176-7359

Cite as: Eren R, Canlan Özaydın B, Göksoy E, Manav Yiğit Z, Gürbüz Özgür B. A Case with Autism Spectrum Disorder and Concomitant Arginase Deficiency. J Behcet Uz Child Hosp. 2024;14(3):195-198

INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by deficits in social communication and interaction, along with restricted interests and repetitive behaviors[1]. ASD may coexist with inborn errors of metabolism (IEM). Increased awareness of both autism and hereditary metabolic diseases has heightened interest in their comorbidities. While the exact prevalence of autism in individuals with hereditary metabolic disorders is not precisely known, it is estimated to be around 2% in individuals with autism[2]. Among these, conditions such as phenylketonuria, histidinemia, creatine deficiency syndromes, adenylosuccinate lyase deficiency, disorders of purine metabolism, mitochondrial diseases, and urea cycle disorders have been identified. The co-occurrence of autism and hereditary metabolic diseases is often associated with dysmorphic features, ataxia, microcephaly, epilepsy, and intellectual disability (ID)[3].

Arginase 1 deficiency (ARG1-D) is a metabolic disorder caused by a defect in the ARG1 enzyme in the final step of the urea cycle, and it is inherited in an autosomal recessive pattern[4]. It is the least common urea cycle disorder, and severe hyperammonemia is not expected. The birth prevalence of arginase deficiency in the United States is recently estimated to be 1.1 cases per live birth[5]. ARG1-D, primarily in early childhood, can cause spasticity, seizures, developmental delay, recurrent vomiting, nausea, and ID, with elevated arginine responsible for neurotoxicity[6].

In this case report, based on the literature data, we aim to highlight the co-occurrence of ASD with a neurometabolic disorder of arginase deficiency.

CASE REPORT

An 11-year-old male patient walking on tiptoes presented to the child psychiatry clinic with difficulties in establishing relationships with his peers, inability to form long sentences, and to eat solid foods.

Medical History

It was revealed that the patient was delivered without complications by caesarean section at full-term, with a birth weight of 4000 grams. Seventeen days after birth he was admitted to the pediatric ward for bronchopneumonia and received respiratory support in the intensive care unit for five days, followed by an 18-day observation in the pediatric ward.

Regarding dietary history, the patient experienced difficulties in swallowing solid foods. When he was given complementary foods, he started to vomit after consuming solid foods. At the age of two, the patient experienced febrile convulsions, and at the age of eight, he had atonic seizures, and received the diagnosis of epilepsy for which he was receiving daily doses of 26 mg/kg levetiracetam.

Developmental Stages

Until the age of two, the patient was breastfed, achieved head control at two months, sat unsupported at eight months, walked, and started speaking single words when he was two years old. It was noted that the patient began walking on tiptoes before the age of two.

Family History

His high school graduate 43-year-old mother was a physically and mentally healthy hosewife. His high school graduate 44-year-old physically and mentally healthy father was engaged in real estate transactions to support the family. The patient who was the second child of the family had a healthy 16-year-old sister. There was no consanguinity between the parents. However there was motor and mental developmental delay in the father's cousins.

Physical Findings

The patient weighed 21 kg [-3.3 standard deviation score (SDS)], with a height of 138 cm (-0.9 SDS), beak nose, retrognathia, slender-long trunk, and restricted dorsiflexion of both feet. Neurologically, there was hyperlaxity in the upper extremities, spastic diplegia, with deep tendon reflexes being normoactive in the upper and hyperactive in the lower extremities. Muscle strength was evaluated as 5/5 in the upper extremities. The patient demonstrated a cross-stepping gait.

Psychiatric Examination

The patient's overall appearance indicated that he was younger than his actual age, and his self-care was age-appropriate. He was conscious, but there was a noticeable lag in perception and judgment compared to his peers. Reduced eye contact, not responding when called, using single words when talking, the presence of stereotypical behaviors such as wing-flapping tremors, echolalia, and engaging in repetitive play were observed. The Schedule for Affective Disorders and Schizophrenia for School-Age Children Present and Lifetime Version-Turkish Adaptation were administered to the patient. The Autism Behavior Checklist, filled out by parents, yielded a score of 52. Following the psychiatric examination, family interviews, and psychometric measurements, the diagnosis of ASD was made based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) diagnostic criteria[1].

Due to dysmorphic findings observed during the physical and neurological examination, the patient was referred to the pediatric health clinic.

Laboratory Tests

Laboratory investigations revealed elevated levels of aspartate aminotransferase (60 U/L), alanine aminotransferase (109 U/L, and ammonia (158 µmol/L). In consideration of these results, the patient was evaluated by a physician specialized in pediatric metabolism disorders. The metabolic laboratory examination revealed significantly high levels of plasma arginine (794 µmmol/L; normal range: 45-125 µmmol/L), and arginine level in a dried blood spot measured by tandem mass spectrometry was 338 µmmol/L (normal range: 10-130 µmmol/L).

Molecular Analysis

The Sophia Clinical Exome Panel, consisting of 4490 genes, was applied to the patient. The data obtained were analyzed using the Sophia-DDM-v4 program. A homozygous missense mutation c.703G>A (p.Gly235Arg) was identified in the *ARG1 gene* (NM_000045.3). This identified alteration was a pathogenic mutation previously reported in the literature[7]. Individuals carrying the G235A alteration have been shown to

lack arginase activity[7]. Targeted mutation analysis was performed on the parents of the patient, revealing that both parents carried the c.703G>A (p.Gly235Arg) mutation in a heterozygous state.

In addition, chromosomal microarray analysis was performed using Illumina Infinium Asian Screening Array-24 v1.0 kit. Data was analyzed with NxClinical program. The result was evaluated as normal.

Considering the patient's medical history, examination, and laboratory findings, arginase deficiency was suspected. The diagnosis was confirmed through molecular analysis. As a treatment, the patient's protein intake was restricted, and sodium benzoate therapy was initiated. According to DSM-5 diagnostic criteria, the patient was diagnosed with ASD developed on the basis of arginase deficiency, with a severity level of 3. In the initial evaluation, the Childhood Autism Rating Scale (CARS) score was 39, indicating severe autism. The patient was referred to a special education and rehabilitation program. After 6 months of special education and rehabilitation, and treatment for arginase deficiency, the case was re-evaluated. According to DSM-5, he received the diagnosis of ASD developed on the basis of arginase deficiency with a severity level of 2, and CARS score of 32.5, indicating mild to moderate autism. Written informed consent was obtained from the patient's parents for the publication of this case.

DISCUSSION

Arginase deficiency is a neurometabolic disorder inherited in an autosomal recessive pattern, manifesting as progressive spastic diplegia. The estimated prevalence is approximately 1 in 363,000 to 2,000,000 live births. Arginase deficiency rarely presents in the neonatal period, and most patients are typically identified as normal in early stages of their lives. The significant feature that distinguishes arginase deficiency from other urea cycle disorders is that it does not present with hyperammonemia, especially in the newborns and infants[5,6]. Initial symptoms usually manifest between 2 and 4 years of age and include stumbling, falling, and delays in growth and development. If not diagnosed, and treated at an early stage, patients may experience progressive spastic diplegia, leading to a gradual loss of developmental milestones. The most prominent symptoms include spastic paraparesis or paraplegia with less impact on the upper extremities, increased deep tendon reflexes, walking on tiptoes, behavioral problems, ID, and seizures. Some patients also exhibit symptoms such as nausea, loss of appetite, and vomiting attacks[6]. Although elevated plasma arginine levels are the most critical diagnostic criterion, elevated liver function test results, decreased blood urea nitrogen, increased plasma citrulline levels, and orotic acid excretion in urine are supportive diagnostic findings. It should be noted that while hyperammonemia is not expected in newborns and infants, it may be observed in the late-childhood stage, particularly during catabolic processes[5,6,8]. Treatment typically involves a diet restricted in protein, supplementation of essential amino acids, and the use of other alternative treatment modalities using sodium benzoate and sodium phenylbutyrate, to remove nitrogen waste. The benefits of treatment have been demonstrated in overcoming behavioral problems and reducing seizures[8].

Various studies have previously investigated the prevalence of neurodevelopmental disorders in individuals with IEM. The best-known inborn metabolic disorders include phenylketonuria, classical homocystinuria, Sanfilippo disease, urea cycle disorders, creatine deficiency syndromes, and purine metabolic pathway disorders[2,9-13].

In a study conducted by Spilioti et al.[9] in Crete, IEM were identified in 5 out of 187 patients with ASD. A study from Turkey, evaluating 237 patients with ASD, detected 6 cases with IEM[11]. In another study conducted in our country, 22 patients with both ASD and IEM were examined in a tertiary care hospital, and none of them were found to have arginase deficiency[10]. In this case report we present the rare coexistence of ASD, with arginase deficiency which was not detected even in large-scale studies.

In the study by Kiykim et al.[13], metabolic diseases were detected in 9 out of 300 patients with ASD, and argininemia was identified in only one case. Although arginase deficiency was not found in this patient, the potential role of elevated arginine in autism was emphasized. In a case from Bahrain, a 14-year-old patient with a diagnosis of ASD was found to have arginase deficiency, and it was reported that there was no significant improvement in ASD scores after treatment[14]. In our patient, a decrease in the severity scores of ASD was observed after treatment. This improvement in indicators of ASD severity over a short period, such as six months, suggests that the likelihood of benefiting from treatment increases, especially when the diagnosis is made at an early stage of the disease.

Bin Sawad et al.[15] systematically reviewed case reports of 157 patients diagnosed with arginase deficiency. Motor

impairments, ID, and seizures, including spasticity, were reported in more than half of the cases examined. Our case also exhibited all of these manifestations. The average age at diagnosis was determined to be 6.4 years, and our case could be considered a late diagnosis compared to this age criterion. Clinical improvement after treatment was reported in only 26% of patients. In our patient, clinical improvement was observed after only 6 months of treatment.

Schiff et al.[12] identified only 2 patients with suspected metabolic disorders among 274 non-syndromic ASD patients. They emphasized the importance of metabolic screening in individuals with dismorphic features and additional neurological symptoms rather than in patients with non-syndromic ID. In our case, spastic diplegia was a prominent non-ASD physical examination finding which underscores the significance of a thorough systemic examination in individuals with ASD.

In cases diagnosed with ASD, especially when there are dysmorphic features and accompanying neurological signs, it is crucial to refer individuals for metabolic screening to the departments of pediatrics and pediatric metabolism. Early diagnosis, coupled with medical intervention, leads to life-saving outcomes serves as a cornerstone in preventing autism and ID, and enhances the effectiveness of special education, contributing positively to the quality of life of the patients.

Ethics

Informed Consent: Written informed consent was obtained from the parents of the patient for the publication of details of the medical case.

Author Contributions

Concept: B.G.Ö., Design: R.E., B.C.Ö., B.G.Ö., Data Collection and Processing: E.G., Z.M.Y., Analysis and Interpretation: E.G., Z.M.Y., Literature Search: R.E., B.C.Ö., Writing: R.E., B.C.Ö., E.G., Z.M.Y., B.G.Ö.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. American Psychiatric Association. DSM-5 Task Force. Diagnostic and statistical manual of mental disorders: DSM-5. 5th ed. Washington, D.C.: American Psychiatric Association; 2013. 947 p. doi: book/10.1176/appi.books.9780890425596
2. Ghaziuddin M, Al-Owain M. Autism spectrum disorders and inborn errors of metabolism: an update. Pediatr Neurol. 2013;49(4):232-6. doi: 10.1016/j.pediatrneurol.2013.05.013
3. Zecavati N, Spence SJ. Neurometabolic disorders and dysfunction in autism spectrum disorders. Curr Neurol Neurosci Rep. 2009;9(2):129-36. doi: 10.1007/s11910-009-0021-x
4. Sin YY, Baron G, Schulze A, Funk CD. Arginase-1 deficiency. J Mol Med (Berl). 2015;93(12):1287-96. doi: 10.1007/s00109-015-1354-3
5. Summar ML, Koelker S, Freedenberg D, Le Mons C, Haberle J, Lee HS, et al. The incidence of urea cycle disorders. Mol Genet Metab. 2013;110(1-2):179-80. doi: 10.1016/j.ymgme.2013.07.008
6. Crombez EA, Cederbaum SD. Hyperargininemia due to liver arginase deficiency. Mol Genet Metab. 2005;84:243-51. doi: 10.1016/j.ymgme.2004.11.004
7. Uchino T, Snyderman SE, Lambert M, Qureshi IA, Shapira SK, Sansaricq C, et al. Molecular basis of phenotypic variation in patients with argininemia. Hum Genet. 1995;96(3):255-60. doi: 10.1007/BF00210403
8. Batshaw ML, MacArthur RB, Tuchman M. Alternative pathway therapy for urea cycle disorders: twenty years later. J Pediatr. 2001;138(Suppl 1):S46-54. doi: 10.1067/mpd.2001.111836
9. Spilioti M, Evangeliou AE, Tramma D, Theodoridou Z, Metaxas S, Michailidi E, et al. Evidence for treatable inborn errors of metabolism in a cohort of 187 Greek patients with autism spectrum disorder (ASD). Front Hum Neurosci. 2013;7:858. doi: 10.3389/fnhum.2013.00858
10. Yoldaş TÇ, Gürbüz BB, Akar HT, Özmert EN, Coşkun T. Autism spectrum disorder in patients with inherited metabolic disorders-a large sample from a tertiary center. Turk J Pediatr. 2021;63(5):767-79. doi: 10.24953/turkjped.2021.05.005
11. İnci A, Özaslan A, Okur İ, Biberoğlu G, Güney E, Ezgü FS, et al. Autism: Screening of inborn errors of metabolism and unexpected results. Autism Res. 2021;14(5):887-96. doi: 10.1002/aur.2486
12. Schiff M, Benoist JF, Aïssaoui S, Boespflug-Tanguy O, Mouren MC, de Baulny HO, et al. Should metabolic diseases be systematically screened in nonsyndromic autism spectrum disorders? PLoS One. 2011;6(7):e21932. doi: 10.1371/journal.pone.0021932
13. Kiykim E, Zeybek CA, Zubarioglu T, Cansever S, Yalcinkaya C, Soyucen E, et al. Inherited metabolic disorders in Turkish patients with autism spectrum disorders. Autism Res. 2016;9(2):217-23. doi: 10.1002/aur.1507
14. Bakhiet M, AlAwadi AMI, AlHammadi MM, Ali MF, Butti N. A case report of neurological complications owing to lately diagnosed hyperargininemia emphasizing the role of national neonatal screening policies in the kingdom of Bahrain. Medicine (Baltimore). 2018;97(20):e10780. doi: 10.1097/MD.0000000000010780
15. Bin Sawad A, Pothukuchy A, Badeaux M, Hodson V, Bubb G, Lindsley K, et al. Natural history of arginase 1 deficiency and the unmet needs of patients: A systematic review of case reports. JIMD Rep. 2022;63(4):330-40. doi: 10.1002/jmd2.12283

2024 Referee Index

Akgün Oral
Ali Yurtseven
Anıl Er
Arzu Yılmaz
Aybüke Akaslan
Aydın Şencan
Ayfer Aydoğdu Çolak
Aylin Özbek
Ayşe Başak Uçan
Ayşegül Efe
Ayşenur Celayir
Caner Baysan
Demet Can
Deniz Yüksel
Ebru Atike Ongun
Ebru Bekiroğlu Yılmaz
Esen Demir
Fatma Sibel Durak
Fazıl Mustafa Gelal
Funda Tüzün Erdoğan
Giray Kolcu
Gonca Özyurt
Hülya Tosun Yıldırım
Hurşit Apa
İlhan Uzel
İlker Devrim
İlker Günay
İlknur Bostancı
İlknur Çağlar
Kamile Ötiken Arıkan
Kenan Karbeyaz
Leman Tekin Orgun
Mehmet Coşkun
Müjgan Sönmez
Nail Özdemir
Nesrin Gülez
Nevin Uzuner
Nihal Dündar
Nuh Yılmaz
Nuket Özkavruk Eliyatkın
Önder Yavaşcan
Orhan Deniz Kara
Özkan İlhan
Özlem Bağ
Pakize Karaoğlu
Safiye Aktaş
Saliha Kanık Yüksek
Sanem Yılmaz
Şanlıay Şahin
Sema Kalkan Uçar
Semra Ayse Hız
Şermin Yalın Sapmaz
Sibel Bozabalı
Sibel Ezberci Acar
Süheyla Sürücüoğlu
Suna Asilsoy
Taliha Öner
Tülin Gökmen Yıldırım
Ümit Naci Gündoğmuş
Utku Karaarslan
Yeşim Oymak

2024 Author Index

2024 Author Index

2024 Subject Index

2024 Subject Index